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1,4-Dichlorobenzene

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TABLE OF CONTENTS

LIST OF TABLES ..... **III**

LIST OF FIGURES ..... **III**

ACRONYMS AND ABBREVIATIONS ..... **III**

CHAPTER 1 SUMMARY TABLES **1**

CHAPTER 2 MAJOR SOURCES AND USE **4**

2.1 SOURCES 4
2.2 USES 5

CHAPTER 3 ACUTE EVALUATION **5**

3.1 HEALTH-BASED ACUTE REV AND ESL 5
3.1.1 Physical/Chemical Properties and Key Studies *6*
3.1.1.1 Physical/Chemical Properties 6
3.1.1.2 Essential Data and Key Studies 6
3.1.1.2.1 Human Studies 6
3.1.1.2.2 Animal Studies 7
3.1.2 Mode-of-Action (MOA) Analysis *8*
3.1.3 Dose Metric *8*
3.1.4 Point-of-Departure (PODs) for the Key Study *8*
3.1.5 Dosimetric Adjustments *8*
3.1.6 Critical Effect and Adjustments of the POD_{HEC} *9*
3.1.6.1 Critical Effect 9
3.1.6.2 Uncertainty Factors (UFs) 9
3.1.7 Health-Based Acute ReV and ^{acute}*ESL* *9*
3.2 WELFARE-BASED ACUTE ESLS 10
3.2.1 Odor Perception *10*
3.2.2 Vegetation Effects *10*
3.3 SHORT-TERM REV AND ^{ACUTE}ESL 11
3.4 ACUTE INHALATION OBSERVED ADVERSE EFFECT LEVEL 11

CHAPTER 4 CHRONIC EVALUATION **11**

4.1 NONCARCINOGENIC POTENTIAL 11
4.1.1 Physical/Chemical Properties and Key Studies *11*
4.1.1.1 Human Studies 11
4.1.1.2 Animal Studies 12
4.1.1.2.1 Key Study – Aiso et al. (2005a) 12
4.1.1.2.1.1 Rat Study (Aiso et al. 2005a) 12
4.1.1.2.1.2 Mouse Study (Aiso et al. 2005a) 13
4.1.1.2.1.3 Most Sensitive Toxic Effect from Aiso et al. (2005a) 14
4.1.1.2.2 Key Study – CPA (1986) 14
4.1.1.2.2.1 Rat Most Sensitive Toxic Effect from CPA (1986) 15
4.1.2 Metabolism and MOA Analysis *16*

4.1.2.2 Metabolism 16
4.1.2.3 Possible MOA for General Systemic Toxicity 18
4.1.3 Dose Metric 19
4.1.4 PODs for Key Studies 19
4.1.4.1 Benchmark Response Level and Critical Effect Size 20
4.1.4.1.1 Benchmark Dose Modeling – Aiso et al. (2005a) 20
4.1.4.1.2 Benchmark Dose Modeling – CPA (1986) 21
4.1.5 Dosimetric Adjustments 22
4.1.5.1 Default Exposure Duration Adjustments 22
4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure 22
4.1.5.2.1 Aiso et al. (2005a) study 22
4.1.5.2.2 CPA (1986) Study 23
4.1.6 Critical Effect and Adjustments of the POD_{HEC} 23
4.1.6.1 Critical Effect 23
4.1.6.2 UFs 23
4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ 24
4.1.8 Comparison of Results 25
4.2 CARCINOGENIC POTENTIAL 26
4.2.1 Carcinogenic Weight-of-Evidence (WOE) 26
4.2.1.1 Other Agencies 26
4.2.1.2 TCEQ Conclusions Regarding Calculation of a Carcinogenic-Based ESL 26
4.2.2 Relevant Data 27
4.2.2.1 Human Data 27
4.2.2.2 Animal Data 27
4.2.2.3 Metabolism of 1,4-DCB Related to Carcinogenicity 28
4.2.3 Carcinogenic MOA 29
4.2.3.1 Genotoxicity 29
4.2.3.2 Mitogenic MOA 29
4.2.4 Justification for Not Developing a Carcinogenic-Based ESL 30
4.2.4.1 Relevance of Mouse Liver Tumors to Humans 31
4.2.4.2 Dose-Response Curve and Linear Low-Dose Extrapolation 31
4.2.4.3 Carcinogenic MOA at the MTD 32
4.2.4.4 Dosimetric Differences in Route-to-Route Extrapolation 32
4.3 WELFARE-BASED CHRONIC ESL 33
4.4 LONG-TERM REV AND ESL 33
4.5 CHRONIC INHALATION OBSERVED ADVERSE EFFECT LEVEL 34

CHAPTER 5 REFERENCES 34

5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT 34
5.2 OTHER STUDIES AND DOCUMENTS REVIEWED BY THE TD 38

APPENDIX 1: BENCHMARK DOSE MODELING RESULTS FOR AISO ET AL. (2005A) 40

APPENDIX 2: BMD MODELING RESULTS FOR CPA (1986) 42

LIST OF TABLES

TABLE 1 AIR MONITORING COMPARISON VALUES (AMCVS) FOR AMBIENT AIR [A, B] 1
TABLE 2 AIR PERMITTING EFFECTS SCREENING LEVELS (ESLS) [A] 2
TABLE 3 CHEMICAL AND PHYSICAL DATA..... 3
TABLE 4 DERIVATION OF THE ACUTE REV AND ^{ACUTE}ESL 10
TABLE 5 DERIVATION OF THE CHRONIC REV AND $^{CHRONIC}ESL_{THRESHOLD(NC)}$ 25

List of Figures

FIGURE 1 PREDOMINANT METABOLIC PATHWAY FOR 1,4-DCB IN HUMANS (USEPA 2006A)..... 18

Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADH	aldehyde dehydrogenase
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
^{0} C	degrees centigrade
BMR	benchmark response
CNS	central nervous system
DSD	development support document
EC_{50}	Effective concentration at a 50% response level
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
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect

${}^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
${}^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
${}^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
${}^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
1,4-DCB	1,4-dichlorobenzene
EU	European Union
GC	gas chromatography
GLP	good laboratory practice
hr	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IC_{50}	Inhibitory concentration at a 50% response level
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LC_{50}	concentration causing lethality in 50% of test animals
LD_{50}	dose causing lethality in 50% of test animals
LOAEL	lowest-observed-adverse-effect-level
LTD	Limited toxicity data
MW	molecular weight
µg	microgram

$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number
NAC	National Advisory Committee
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OAEL	Observed adverse effect level
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
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
RD_{50}	50% reduction in respiration rate
ReV	reference value
RGDR	regional gas dose ratio
ROS	Reactive oxygen species
RP	Relative potency
RP_{GM}	Geometric mean of relative potency endpoints
SA	surface area
SD	Sprague-Dawley
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
USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of 1,4-dichlorobenzene (1,4-DCB). Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on 1,4-DCB's physical/chemical data.

Table 1 Air Monitoring Comparison Values (AMCVs) for Ambient Air [a, b]

Short-Term Values	**Concentration**	**Notes**
Acute ReV	**Short-Term Health** 3,000 µg/m^3 (500 ppb)	**Critical Effect:** eye and nose irritation in exposed workers
$^{acute}ESL_{odor}$	**Odor** 720 µg/m^3 (120 ppb)	50% odor detection threshold
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**Long-Term Health** 530 µg/m^3 (89 ppb)	**Critical Effect:** increases in nasal olfactory epithelial lesions in female rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data inadequate
$^{chronic}ESL_{veg}$	- - -	No data found

[a] These health- and welfare-based values only apply to 1,4-DCB as a vapor.

[b] 1,4-DCB is not monitored for by the TCEQ's ambient air monitoring program (TCEQ's ambient air monitoring program), so currently no ambient air data (i.e., peaks, annual averages, trends, etc.) are available to assess 1,4-DCB concentrations in Texas ambient air.

Table 2 Air Permitting Effects Screening Levels (ESLs) [a]

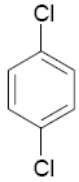
Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	900 µg/m^3 (150 ppb) [b]	**Critical Effect:** eye and nose irritation in exposed workers
$^{acute}ESL_{odor}$	**Short-Term ESL for Air Permit Reviews** 720 µg/m^3 (120 ppb)	50% odor detection threshold
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**Long-Term ESL for Air Permit Reviews** 160 µg/m^3 (27 ppb) [c]	**Critical Effect:** increases in nasal olfactory epithelial lesions in female rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data inadequate
$^{chronic}ESL_{veg}$	- - -	No data found

[a] These health- and welfare-based values only apply to 1,4-DCB as a vapor.

[b] Based on the acute ReV of 3,000 µg/m^3 (500 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[c] Based on the chronic ReV of 530 µg/m^3 (89 ppb)multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

Table 3 Chemical and Physical Data

Parameter	**Value**	**Reference**
Molecular Formula	$C_6H_4Cl_2$ 	ATSDR (2006)
Molecular Weight	147.00 (g/mole)	TRRP (2006)
Physical State	solid	ATSDR (2006)
Color	colorless or white	ATSDR (2006)
Odor	mothball-like; penetrating	ATSDR (2006)
CAS Registry Number	106-46-7	TRRP (2006)
Synonyms and Trade Names	Synonyms: para-dichlorobenzene, p-dichlorobenzene, p-chlorophenyl chloride, PDB, PDCB, p-dichlorobenzol; Trade Names: Paracide, Paradow, Paradi, Santochlor, Paramoth, paranuggets, Parazene, Persia-parazol, Para crystals, Global, Evola, Di-chloricide	ATSDR (2006)
Solubility in water	73.8 mg/L	TRRP (2006)
Log K_{ow}	3.28	TRRP (2006)
Vapor Pressure	1.06 mm Hg at 25°C	TRRP (2006)
Vapor Density (air = 1)	5.08 g/L	HSDB (2007)
Density (water = 1)	1.46 g/ml at 20° C	ATSDR (2006)
Melting Point	52.7^{o} C	ATSDR (2006)
Boiling Point	174° C	ATSDR (2006)
Conversion Factors	1 µg/m^3 = 0.166 ppb @ 25°C 1 ppb = 6.01 µg/m^3	ATSDR (2006)

Chapter 2 Major Sources and Use

2.1 Sources

General information on 1,4-dichlorobenzene (1,4-DCB) sources, taken from the Agency for Toxic Substances and Disease Registry (ATSDR 2006), is given below.

> Humans are exposed to 1,4-DCB mainly by breathing vapors from 1,4-DCB products used in the home, such as mothballs and toilet-deodorizer blocks. Reported levels of 1,4-DCB in some homes and public restrooms have ranged from 0.291 to 272 parts of 1,4-DCB per billion parts (ppb) of air. Outdoor levels of 1,4-DCB range from 0.01 to 1 ppb and are much lower than levels in homes and buildings. The average daily adult intake of 1,4-DCB is about 35 micrograms (µg), which comes mainly from breathing 1,4-DCB vapors released from products in homes and businesses. Individuals can be occupationally exposed to DCBs in workplace air at much higher levels than the general public is exposed. Levels measured in the air of factories that make or process 1,4-DCB products have ranged from 5.6 to 748 ppm of air. In addition, people who live or work near industrial facilities or hazardous waste sites that have high levels of DCBs may have greater exposure to these compounds due to emissions from the facilities and waste sites. People who work or live in buildings where air fresheners, toilet block deodorants, or moth balls containing 1,4-DCB are used also are expected to have a higher exposure to this compound, which could occur from skin contact as well as by breathing.
>
> Because 1,4-DCB is a volatile substance that sublimes at room temperature, most environmental releases are to the atmosphere. In 1972, 70–90% of the annual U.S. production of 1,4-DCB was estimated to have been released into the atmosphere primarily as a result of its use in toilet bowl and garbage deodorants, and its use in moth control as a fumigant (IARC 1982). It has been estimated that about 40% of the domestic use of 1,4-DCB is for space deodorants moth repellents (CMR 1999). Assuming that 90% of the space deodorants and all of the moth repellents are released to the atmosphere (EPA 1981a), and using current production data (50–100 million pounds or 23,000–45,000 metric tons) (EPA 2002e), about 20–40 million pounds (9,000–18,000 metric tons) of 1,4-DCB were released to the air in 1994 from these sources. 1,4-DCB may also be emitted to air from other sources, such as hazardous waste sites (EPA 1981a), during its use as a fumigant (EPA 1981a), or from emissions from waste incinerator facilities (Jay and Stieglitz 1995). These emissions are likely to be a minor contribution to the total atmospheric loading of 1,4-DCB, but may be locally important. There are no known natural sources of 1,4-DCB (IARC 1999).
>
> According to the TRI, in 2003, a total of 96,993 pounds (44 metric tons) of 1,4-DCB was released to the environment from 21 large processing facilities (TRI03 2005). Table 6-3 lists amounts released from these facilities. Of this total, an estimated 85,463 pounds (39 metric tons) were released to air, 815 pounds (0.4 metric tons) were released to water, 270

> pounds (0.1 metric tons) were released to land, and 10,408 pounds (5 metric tons) were released via underground injection. The total amount of 1,4-DCB released on-site was estimated as 96,696 pounds (44 metric tons). The total amount released off-site was estimated as 297 pounds (0.1 metric tons) (TRI03 2005).

According to Table 6-3 of ATSDR (2006), air emissions of 1,4-DCB from Texas facilities accounted for approximately 17% of the total air emissions reported for the 2003 TRI. Some air fresheners and toilet deodorant blocks have been reported to contain approximately 99% 1,4-DCB (NICNAS 2000).

2.2 Uses

Information on 1,4-DCB uses, taken from ATSDR (2006), is given below.

> For the past 20 years, 1,4-DCB has been used principally (25–55% of all uses) as a space deodorant for toilets and refuse containers, and as a fumigant for control of moths, molds, and mildews. In recent years, the use of 1,4-DCB in the production of polyphenylene sulfide (PPS) resin has increased steadily (25–50% of its total use). 1,4-DCB is also used as an intermediate in the production of other chemicals such as 1,2,4-trichlorobenzene (approximately 10%). Minor uses of 1,4-DCB include its use in the control of certain tree-boring insects and ants, and in the control of blue mold in tobacco seed beds (CMR 1999; HSDB 2005).
>
> Because of widespread use as a moth repellant and deodorant, there is potential for relatively high indoor exposure. In 1987, USEPA's Total Exposure Assessment Methodology study found 1,4-DCB in the air of 80% of the homes surveyed, with mean personal (21 µg/m^3) and indoor (30 µg/m^3) concentrations being higher than outdoor levels (2.0 µg/m^3) (Elliot et al. 2006). The common presence of 1,4-DCB in indoor air results in the nearly ubiquitous detection of it in human breath, blood, urine, adipose tissue, and breast milk (Tables 5 and 6 in Aronson et al. 2007). In regard to blood levels, 96% of subjects in a subset of the Third National Health and Nutrition Examination Survey (NHANES III 1988-1994) had detectable 1,4-DCB levels in the blood (Elliot et al. 2006). A mean 1,4-DCB blood concentration of 2.1 µg/L and a mean urinary 2,5-dichlorophenol (metabolite) level of 200 µg/L were reported for the US general population (Aiso et al. 2005a). Median and 90th percentile 1,4-DCB blood concentrations of 0.30-0.33 and 3.89-4.83 µg/L, respectively, were reported for the NHANES III Priority Toxicant Reference Range Study (Elliot et al. 2006).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

The key study discussed in this section was initially identified through review of ATSDR (2006). A review of the scientific literature since 2005 by the Toxicology Division (TD) did not identify

any new toxicity studies for development of the acute Reference Value (acute ReV) and acute Effects Screening Level (^{acute}ESL).

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

The main chemical and physical properties of 1,4-DCB are summarized in Table 3. 1,4-DCB is a solid, volatile chemical that sublimes (i.e., converts directly from a solid to a gas) at room temperature (ATSDR 2006). Therefore, depending upon the process (e.g., sublimation, heating, mechanical), it may be emitted as a vapor or particulate. *This document only evaluates 1,4-DCB as a vapor as toxicity data for 1,4-DCB as particulate are lacking.*

3.1.1.2 Essential Data and Key Studies

A summary of human and animal studies may be found in ATSDR (2006).

3.1.1.2.1 Human Studies

Available toxicological information on humans exposed to 1,4-DCB via inhalation is limited. Case reports of people who inhaled 1,4-DCB indicate that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (ATSDR 2006). While 1,4-DCB is capable of producing systemic toxicity at relatively high concentrations, the critical effects for acute (and longer-term) inhalation exposure to 1,4-DCB in humans are eye and nose irritation (ATSDR 2006). Human data on the acute irritant effects of 1,4-DCB are available and preferred over animal study data for the calculation of an acute ReV and ^{acute}ESL.

Human data from Hollingsworth et al. (1956) will be utilized as the key study for derivation of the acute ReV and ^{acute}ESL. Although workers were exposed for durations longer than an acute exposure, observations in these workers provide information relevant to eye and nose irritation experienced during short-term exposures. The results of this study indicate that nose and eye irritation are critical effects of acute and repeated exposures to 1,4-DCB in humans. Human data from Hollingsworth et al. (1956) are the basis for ATSDR's acute inhalation minimal risk level (MRL) and largely the basis for the current occupational Threshold Limit Value - Time Weighted Average (TLV-TWA) (ATSDR 2006, ACGIH 2001).

In Hollingsworth et al. (1956), occupational health examinations were conducted periodically on 58 male workers involved in the handling of 1,4-DCB. Worker exposure was generally for 8 hour (h)/day, 5 days/week, continually or intermittently for periods of 8 months to 25 years (mean of 4.75 years). The study summarizes the effects of different workplace exposure levels on eye and nose irritation based on three industrial hygiene surveys of 1,4-DCB concentrations in workroom air. The periodic medical evaluations included examination of the eyes, blood cell counts (i.e., RBC, WBC, differential), hemoglobin, hematocrit, mean corpuscular volume, blood

urea nitrogen, sedimentation rate, and urinalysis (ATSDR 2006). The results of the three surveys are as follows:

- the first survey indicated painful eye/nose irritation in workers exposed at 80-160 ppm, with greater than 160 ppm being intolerable to unacclimated workers, and the odor was found to be faint at 15–30 ppm and strong at 30–60 ppm;
- the second survey showed a mean of 90 ppm to be acceptable to workers, with a mean of 380 ppm being uncomfortable for acclimated workers and intolerable for unacclimated workers;
- the third survey was conducted after extensive operating procedure and equipment changes and showed increased eye/nose irritation at 50-170 ppm with a mean of 105 ppm, with no complaints occurring at 15-85 ppm with a mean of 45 ppm.

The authors concluded that painful irritation of the eyes and nose was usually experienced at 50–80 ppm, becoming severe for unacclimated workers at about 160 ppm. Concentrations above 160 ppm caused severe irritation and were considered intolerable by unacclimated persons. The odor and irritation properties were considered to be fairly good acute warning properties and were expected to prevent excessive exposures. No cataracts or other lens changes in the eyes, or effects on clinical indices, were attributable to exposure (ATSDR 2006).

Based on Hollingsworth et al. (1956), TD conservatively designates 50 ppm as the minimal lowest-observed-adverse-effect-level (LOAEL) for nose and eye irritation as it is the lowest concentration in the range associated with eye/nose irritation based on the three surveys. The no-observed-adverse-effect-level (NOAEL) is conservatively considered to be 15 ppm as it is the lowest concentration in the range not associated with eye/nose irritation in the third survey, which had a reasonably narrow exposure range (15-85 ppm). *The NOAEL of 15 ppm (90 mg/m^3) will be used as the point-of-departure (POD) for derivation of the acute ReV and ESL.* Use of the NOAEL of 15 ppm as a POD is almost identical to use of the minimal LOAEL of 50 ppm divided by a LOAEL-to-NOAEL uncertainty factor of 3 (i.e., 50/3 = 16.7 ppm).

3.1.1.2.2 Animal Studies

Based on available data, the lung appears to be the critical target organ in laboratory animals. For example, short-term inhalation exposure of rats and guinea pigs to 1,4-DCB produced mild histological effects in the lung (i.e., interstitial edema, congestion, alveolar hemorrhage) at a LOAEL of approximately 173 ppm (7 h/day, 5 days/week, for 16 days) (Hollingsworth et al. 1956). However, human data are available and preferred over animal studies for calculation of the acute ReV and ^{acute}ESL. Therefore, this document focuses on relevant human studies (see above). Please refer to ATSDR (2006) for a discussion of other short-term animal inhalation studies.

A reproductive/developmental study was conducted by the Chlorobenzene Producers Association (CPA 1986). The CPA (1986) study is a two-generation reproductive study in Sprague-Dawley rats conducted according to USEPA good laboratory practice standards (40

CFR Part 160) and is discussed in detail in Section 4.1.1.2.2. Results from this study indicate that 1,4-DCB is not a developmental toxin.

3.1.2 Mode-of-Action (MOA) Analysis

An MOA is generally defined as a sequence of key events and processes (starting with interaction of an agent with a cell and proceeding through operational and anatomical changes) resulting in toxicity (USEPA 2005). At sufficiently high air concentrations, 1,4-DCB and many other compounds are irritating to the eyes and nose.

In regards to the MOA, irritation may be sensory and/or pathological in nature (Arts et al. 2006). Chemically-induced sensory irritation involves interaction with local nerve endings (e.g., nervus trigeminus), and is also called chemosensory irritation or trigeminal stimulation. Sensory irritation can also involve the chemical stimulation of the vagal or glossopharyngeal nerves. The free nerve endings of the trigeminal system innervate the walls of the nasal passages and eyes and may be stimulated, producing a response. For example, nasal pungency or watery/prickly eyes may occur due to exposure to sufficiently high concentrations of a large variety of volatile chemicals. Chemically-induced trigeminal nerve stimulation contributes to a sensation of general nasal and eye irritability, but does not necessarily lead to pathological changes such as cell or tissue damage (Arts et al. 2006). Paustenbach (2000) defines sensory irritants as chemicals that produce temporary and undesirable effects on the eyes, nose, or throat. In the key study, sensory irritation induced by 1,4-DCB consists of eye and nose irritation, which are threshold effects at the point-of-contact.

3.1.3 Dose Metric

In the key study (Hollingsworth et al. 1956), data on 1,4-DCB air concentration are available. 1,4-DCB air concentration is the most appropriate dose metric for the acute evaluation as concentration is the dominant determinant of irritation in acute exposure studies (TCEQ 2012).

3.1.4 Point-of-Departure (PODs) for the Key Study

The NOAEL of 15 ppm (analytical concentration) from the Hollingsworth et al. (1956) key study will be used as the human point-of-departure (POD_{HEC}) in calculation of the acute ReV and ${}^{acute}ESL$.

3.1.5 Dosimetric Adjustments

Since the acute irritant effects of 1,4-DCB appear to be primarily concentration dependent, exposure duration adjustments were not used to extrapolate from an 8-h workday to a 1-h exposure duration, consistent with TCEQ (2012). Therefore, the POD_{HEC} = 15 ppm (NOAEL).

3.1.6 Critical Effect and Adjustments of the POD_{HEC}

3.1.6.1 Critical Effect

The most sensitive endpoint for human exposure to 1,4-DCB (short- and long-term) is irritation of the eyes and nose (ATSDR 2006). Sensory irritation of the eye and nose is the specific critical effect of 1,4-DCB exposure in the key study (Hollingsworth et al. 1956).

3.1.6.2 Uncertainty Factors (UFs)

Sensory irritation is a threshold effect (Section 3.1.2). For noncarcinogenic effects which exhibit a threshold MOA (i.e., nonlinear), a POD_{HEC} is determined and appropriate UFs are applied to derive a ReV (TCEQ 2012).

The NOAEL from Hollingsworth et al. (1956) of 15 ppm was used as the POD_{HEC} and divided by the following uncertainty factors (UFs): 10 for intrahuman variability (UF_H) and 3 for database uncertainly (UF_D) (total UF = 30).

- A UF_H of 10 was used for intrahuman variability since the irritant effects were observed in a population of workers which was not known to include potentially sensitive subpopulations; workers sensitive to the irritant effects of 1,4-DCB may have left the exposed-worker study population; workers may become acclimated to 1,4-DCB exposure; and population variation has been observed in sensitivity to other irritants (e.g., formaldehyde).

- A UF_D of 3 was used because the acute toxicological database for 1,4-DCB is somewhat limited in both humans and animals (see Section 3.12.2 of ATSDR 2006).

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

As discussed in the previous section, UFs are applied to the key study (Hollingsworth et al. 1956) POD_{HEC} to derive the acute ReV:

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D)$$
$$= 15 \text{ ppm} / (10 \times 3)$$
$$= 0.50 \text{ ppm (500 ppb)}$$

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then multiplied by 0.3 to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV for 1,4-DCB is 0.50 ppm, or 500 ppb (3,000 µg/m^3). At the target hazard quotient of 0.3, the ^{acute}ESL is 150 ppb (900 µg/m^3) (Table 4).

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

Parameters	**Summary**
Study	Hollingsworth et al. (1956)
Study population	58 occupationally-exposed workers
Study quality	Medium
Exposure Method	inhalation
LOAEL	30 ppm
NOAEL	15 ppm
Critical Effects	Eye and nose irritation
POD_{HEC}	15 ppm
Exposure Duration	8 h/day
Extrapolation to 1 h	Not Applicable since effects are concentration dependent
Extrapolated 1 h concentration	15 ppm
Total UFs	30
Intraspecies UF	*10*
Incomplete Database UF *Database Quality*	*3* *Medium*
Acute ReV [1 h] (HQ = 1)	**3,000 µg/m^3 (500 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**900 µg/m^3 (150 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

1,4-DCB has a mothball-like, penetrating odor and is used as a room space deodorant (ATSDR 2006). Punter (1983) provides odor threshold information for 1,4-DCB and is a Level 3 odor source (TCEQ 2012). Punter (1983) lists a 50% odor detection threshold of 121 ppb for 1,4-DCB. Rounding to two significant figures, 120 ppb (720 µg/m^3) will be used as the $^{acute}ESL_{odor}$. Since the perception of odor is a concentration-dependent effect, the same $^{acute}ESL_{odor}$ is assigned to all averaging times.

3.2.2 Vegetation Effects

No data were found on the potential effects of 1,4-DCB on vegetation.

3.3 Short-Term ReV and ^{acute}ESL

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

- acute ReV = 3,000 µg/m^3 (500 ppb)
- ^{acute}ESL = 900 µg/m^3 (150 ppb)
- ^{acute}ESL$_{odor}$ = 720 µg/m^3 (120 ppb)

The acute ReV for 1,4-DCB is 3,000 µg/m^3 (500 ppb). The critical short-term ESL applicable to air permit reviews is the odor-based ^{acute}ESL$_{odor}$ of 720 µg/m^3 (120 ppb) as it is lower than the health-based ^{acute}ESL of 900 µg/m^3 (150 ppb) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 30,000 ppb **(**Hollingsworth et al. 1956). The LOAEL$_{HEC}$ determined from human studies, where eye and nose irritation occurred in some individuals, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the acute observed adverse effect level and the ReV is a factor of 60. (Table 4).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of 1,4-DCB are discussed in Chapter 3. Discussions of human and animal studies relevant for the chronic noncarcinogenic evaluation and the key studies used for derivation of the chronic noncarcinogenic ReV and ESL (^{chronic}ESL$_{threshold(nc)}$) are presented below.

4.1.1.1 Human Studies

While human data are preferred for derivation of a chronic noncarcinogenic ReV and ^{chronic}ESL$_{threshold(nc)}$, information on the long-term toxicity of inhaled 1,4-DCB in humans is limited. No well-controlled epidemiological studies have been conducted (NICNAS 2000). In Hollingsworth et al. (1956), periodic health examinations of workers exposed to 1,4-DCB for an average of 4.75 years (range of 8 months to 25 years) revealed no changes in standard blood and urine indices. Painful eye and nose irritation was usually experienced at 50–80 ppm, although the irritation threshold was higher in workers acclimated to exposure (80–160 ppm). Concentrations

exceeding 160 ppm caused severe irritation and were considered intolerable to workers not adapted to it. Occasional eye examinations showed no cataracts or any other lens changes. Nose and eye irritation findings in humans are consistent with nasal effects observed in chronically exposed animals. The data from the Hollingsworth et al. (1956) study are inadequate, however, for derivation of a chronic ReV and $^{chronic}ESL_{threshold(nc)}$ due to poor characterization of long-term exposure levels, insufficient investigation of systemic health endpoints, reporting deficiencies, and other study deficiencies. While no human study could be identified for derivation of the chronic ReV and $^{chronic}ESL_{threshold(nc)}$, refer to ATSDR (2006) for available information regarding the potential health effects of long-term 1,4-DCB inhalation exposure in humans.

4.1.1.2 Animal Studies

In regard to animal data, important information on the long-term inhalation toxicity of 1,4-DCB is available from a chronic rat and mouse study (Aiso et al. 2005a, also presented in a preliminary, non-peer reviewed summary as Japan Bioassay Research Center 1995) and a two-generation reproductive rat study (CPA 1986). Aiso et al. (2005a) and CPA (1986) will be used as key studies in the derivation of a chronic noncarcinogenic ReV and $^{chronic}ESL_{threshold(nc)}$.

4.1.1.2.1 Key Study – Aiso et al. (2005a)

In the Aiso et al. (2005a) study, groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF1 mice were exposed to 1,4-DCB at target concentrations of 0, 20, 75, or 300 ppm for 6 h/day, 5 days/week for 104 weeks. The study was conducted in accordance with the Organization for the Economic Cooperation and Development (OECD) Guideline for Testing of Chemicals 453: Combined Chronic Toxicity/Carcinogenicity Studies, and the OECD Principles of Good Laboratory Practices. The toxicological endpoints evaluated included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), hematology, blood biochemistry, and urinalysis indices (evaluated at the end of the study). Comprehensive gross pathological and histological evaluations and selected organ weight measurements (i.e., liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, ovary) were conducted on all animals at the end of the study or at the time of unscheduled death. Histological examinations included reproductive system tissues in both sexes (i.e., testis, epididymis, seminal vesicle, prostate, ovary, uterus, vagina, and mammary gland), but there were no exposure-related adverse findings in either species or sex (ATSDR 2006). *As discussed in the following sections, the study identified a NOAEL of 19.8 ppm and a LOAEL of 74.8 ppm for dose-related nasal lesions (eosinophilic globules) in the olfactory epithelium of female rats). The study was used by ATSDR (2006) as the basis for their chronic inhalation MRL and by USEPA (2006a) as the basis for their draft RfC.*

4.1.1.2.1.1 Rat Study (Aiso et al. 2005a)

For rats, the analytical mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study. The number of male rats surviving to scheduled termination was significantly reduced at 298.4 ppm. There were no exposure-related decreases in survival in female rats, or effects on growth or food consumption in either sex. At 298.4 ppm, changes in

various hematological and blood biochemical indices occurred in males (i.e., mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, calcium) and females (i.e., total protein, total bilirubin, blood urea nitrogen, and potassium). However, a lack of numerical data and statistical analysis precludes interpretations of significance for these hematological endpoints (ATSDR 2006). Absolute and relative liver weights in both sexes, and kidney weights in males, were significantly increased at 298.4 ppm.

Both nasal and kidney lesions were reported. Kidney lesions occurred only in male rats at 298.4 ppm, and included significantly increased incidences of mineralization of the renal papilla (0/50, 1/50, 0/50, 41/50) and hyperplasia of the urothelium (7/50, 8/50, 13/50, 32/50). The nasal lesions that occurred mainly included increased incidences of eosinophilic globules in the olfactory epithelium (moderate or greater severity) in males at 298.4 ppm and females at ≥ 74.8 ppm. The term "eosinophilic" refers to the affinity of these lesions for eosin stain. Incidences of this nasal lesion (moderate or greater severity) at 0, 19.8, 74.8, and 298.4 ppm were 1/50, 2/50, 2/50, and 7/50 in males, and 28/50, 29/50, 39/50, and 47/50 in females, respectively. According to statistical analyses conducted by ATSDR (2006), the increased incidences of eosinophilic globules in the olfactory epithelium were statistically significant ($p \leq 0.05$) at ≥ 74.8 ppm in females and at 298.4 ppm in males, and there was a trend of increasing response with increasing dose based on the female rat data. Eosinophilic globules (eosinophilic intracytoplasmic proteinaceous accumulations) in the olfactory epithelium are indicative of degenerative changes (dilated endoplasmic reticulum containing proteinaceous material) (USEPA 2006b, Dungworth et al. 2001) and are increased in association with toxic effects on the nasal mucosa (Renne et al. 2007). Additionally, they have been reported to contain proteins which may play an important role in the regeneration of olfactory epithelium following toxicant-induced injury (Harkema et al. 2006). *The increased incidence of this nasal lesion in female rats at ≥ 74.8 ppm forms the basis of the rat and overall LOAEL from this study.* Other nasal lesions that were significantly increased in female rats at 298.4 ppm were eosinophilic globules in the respiratory epithelium (11/50, 10/50, 14/50, 38/50) and respiratory metaplasia in the nasal gland (5/50, 4/50, 4/50, 33/50).

4.1.1.2.1.2 Mouse Study (Aiso et al. 2005a)

For mice, the analytical mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm. Survival was significantly reduced in male mice at 298.3 ppm (due to an increase in liver tumor deaths), but was comparable to controls in female mice. At 298.3 ppm, absolute and relative liver and kidney weights were significantly increased in both sexes, and terminal body weight was significantly reduced in males. Additionally, at 298.3 ppm, changes in various hematological and blood biochemical indices occurred in both sexes (i.e., total cholesterol, serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], alkaline phosphatase [AP]), but certain changes occurred only in females (i.e., platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, calcium). However, a lack of both numerical data and statistical analysis precludes interpretation of these endpoints (ATSDR 2006). Histopathological changes in the nasal cavity, liver, and testes were also reported. The nasal lesions included significantly increased incidences of respiratory

metaplasia (normal to abnormal cell type changes) in the nasal gland (moderate severity) in males at 74.8 ppm (9/49, 12/49, 18/50, 11/49), and significantly increased incidences of respiratory metaplasia in the olfactory epithelium (slight severity) in males at 74.8 ppm (23/49, 30/49, 37/50, 22/49) and females at 298.3 ppm (7/50, 6/50, 2/49, 20/50). These effects in males, however, were not dose-related (i.e., incidences were increased at 74.8 ppm but not at 298.3 ppm).

The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 298.3 ppm (0/49, 0/49, 0/50, 34/49). Testicular mineralization was significantly increased in males at ≥ 74.8 ppm (27/49, 35/49, 42/50, 41/49). However, ATSDR (2006) reports that testicular mineralization was not considered to be a toxicologically significant effect because: (1) no signs of testicular toxicity were observed in mice exposed for 13 weeks (Aiso et al. 2005b); and (2) it was confined to the testicular capsules and testicular blood vessels and not observed in the testicular parenchyma, indicating that it is a finding commonly observed in aged mice independent of exposure to 1,4-DCB. *The LOAEL for mice from the Aiso et al. (2005a) study is 298.3 ppm based on multiple adverse effects, most notable for this noncarcinogenic assessment, increased liver weight in both sexes (see last paragraph of Section 4.1.4.1).*

4.1.1.2.1.3 Most Sensitive Toxic Effect from Aiso et al. (2005a)

The study authors concluded that nasal lesions were the most sensitive endpoint of chronic inhalation toxicity. More specifically, the most sensitive toxic effects in the most sensitive species and sex of this key study (Aiso et al. 2005a, also reported as Japan Bioassay Research Center 1995) are eosinophilic globules of moderate or greater severity in the nasal olfactory epithelium of female rats. *The NOAEL and LOAEL for these nasal lesions are 19.8 and 74.8 ppm, respectively.*

4.1.1.2.2 Key Study – CPA (1986)

CPA (1986) is a two-generation reproductive study in Sprague-Dawley rats conducted according to USEPA's good laboratory practice standards (40 CFR Part 160). This study was used by USEPA (1996) as the basis for their current reference concentration (RfC), although the draft RfC document (USEPA 2006a) uses the Aiso et al. (2005a) study. Parental animals (F_0) were exposed to 1,4-DCB vapor (28 rats per sex per exposure group) at target concentrations of 0, 50, 150, or 450 ppm for 10 weeks, 6 h/day, 7 days/week. Analytical mean exposure concentrations were 0, 66.3, 211, and 538 ppm, respectively. Following the initial 10-week exposure, F_0 rats were mated for 3 weeks. Exposure of F_0 females continued through mating and the first 19 days of gestation, and resumed for postnatal days 5 through 27. After F_1 pups were weaned, F_0 females were sacrificed, and tissues from the high exposure and control groups were examined for histological lesions. Exposure of F_0 males continued through the mating period, after which they were sacrificed and tissues from the high exposure and control groups were examined for histological lesions. Livers and kidneys from F_0 males and females in the low and mid exposure groups were also examined histologically.

Randomly selected weanlings of the F_1 generation (28 rats per sex per exposure group) were

exposed to the same 1,4-DCB concentrations as their parents for 11 weeks and mated to produce F_2 generation offspring. F_1 generation weanlings not selected for exposure and mating were sacrificed and examined for gross lesions. F_1 parental rats were sacrificed and examined as described above for the F_0 parental rats. All F_2 generation pups were sacrificed and examined at weaning.

In regard to potential reproductive/developmental effects, there was a statistically significant decrease in live births and pup survival and pup weights for both the F_1 and F_2 generations at 538 ppm. However, effects on body weight, liver and kidney weight, and hepatocellular hypertrophy were found in the adult rats at 211 and 538 ppm, indicative of toxicity to the parental animals. The authors of CPA (1986) concluded that parental toxicity was the cause of the increased risk to offspring rather than the inherent effects of 1,4-DCB on reproduction/development. Exposure to 1,4-DCB is not known to impair reproduction or fetal development in animals at exposure levels below those which cause maternal toxicity (ATSDR 2006). Therefore, 1,4-DCB was not considered by TD to cause developmental effects.

Effects observed in this study included:

- Increased liver and kidney weights were observed in F_0 males in the 211 and 538 ppm exposure groups, and in F_0 females in the 538 ppm exposure group only. F_0 males also had significantly increased liver weight relative to brain weight at 211 and 538 ppm;
- F_0 females had decreased gestational body weight on day 20 at 211 and 538 ppm, and occasionally had decreased weight gain at 538 ppm. F_0 males had reduced body weight and weight gain at 538 ppm;
- Increased liver weights were observed in F_1 males and females at 538 ppm;
- F_1 males experienced reduced body weight and weight gain at 538 ppm, sporadic changes (increases/decreases) in weight gain at 211 ppm, and F_1 females had reduced body weights at 538 ppm;
- At 538 ppm, treatment-related clinical signs in both F_1 males and females included hypoactivity, ataxia (e.g., incoordination, unsteadiness), tremors, unkept appearance, lacrimation, periocular/perioral encrustation, etc.;
- Histological observations showed significant increases in the incidence of hepatocellular hypertrophy (i.e., increased cell volume) in parental F_0 and F_1 males and females at 538 ppm.

All dose levels caused hyaline droplet nephrosis in post-puberal males, which was associated with the formation of alpha-2µ-globulin (i.e., the lesions observed in male rats exposed to 1,4-DCB met the criteria for alpha-2µ-globulin nephropathy). The formation of alpha-2µ-globulin is recognized as an abnormality specific for male rats and does not have significance relative to human health (USEPA 1991, Charbonneau et al. 1989).

4.1.1.2.2.1 Rat Most Sensitive Toxic Effect from CPA (1986)

The NOAEL for adult rats from CPA (1986) is 66.3 ppm, excluding male rat alpha-2µ-globulin

nephropathy which is irrelevant to humans. For offspring, the NOAEL is 211 ppm. *The LOAEL of 211 ppm is based on significant increases in liver weights in F_0 (parental) males, consistent with USEPA (1996), since male rats were more sensitive than females to 1,4-DCB-induced changes in liver weight.* Increased kidney weight in male rats was not considered in selection of the LOAEL as hyaline droplet nephropathy was present at all exposure concentrations, is unique to male rats, and affected male kidney weight according to the study authors. Various case reports of human poisonings have also reported effects on the liver (NICNAS 2000), although these reports are not useful for quantitative risk assessment due to lack of exposure concentration data, cause-effect not being established, etc.

4.1.2 Metabolism and MOA Analysis

4.1.2.2 Metabolism

ATSDR (2006) provides the following discussion of 1,4-DCB metabolism. Figure 1, which was taken from USEPA (2006a), depicts the predominant metabolic pathway of 1,4-DCB in humans.

> In general, the basic steps in metabolism of 1,4-DCB are similar to those of the other DCB isomers. The initial metabolic step is oxidation by cytochrome P-450, primarily P4502E1, to an epoxide and further to 2,5-dichlorophenol. The dichlorophenol may be further oxidized to dichlorocatechols, or possibly a dichlorohydroquinone, or may be conjugated by several phase II metabolism pathways. Support for the cytochrome P-450-mediated oxidation of 1,4-dichlorophenol, and subsequent conjugation reactions, comes from studies in isolated microsomes, liver slices, and exposures *in vivo*.
>
> Fisher et al. (1990) reported that in rat liver slices, the majority (> 60%) of 1,4-DCB was found conjugated to glutathione, or as a cysteine conjugate, with small amounts of the sulfate detected as well (~10% of total metabolites). In human liver slices, the pattern was different, with glutathione still being the predominant metabolite (~55%), but with an approximately equal distribution of glucuronide and sulfate conjugates (22–24%). In a later study, Fisher et al. (1995) reported that the total metabolism of 1,4-DCB was similar in liver slices from F344 rats, Sprague-Dawley rats, and humans. Human liver slices formed greater levels (~20–50%) of glucuronide conjugates of 1,4-DCB than rat liver slices; levels of formation of sulphatase and glutathione conjugates were similar in rats and humans (Fisher et al. 1995).
>
> Incubation of 1,4-DCB with microsomes from cells expressing human cytochrome P-450 enzymes indicated that the 2,5-dichlorophenol was the only isomer formed, and that cytochrome P4502E1 was the most active isozyme in its formation (Bogaards et al. 1995; Hissink et al. 1996a, 1996b). In human microsomes, metabolism of 1,4-DCB was lower than in rodents, with 2,5-dichlorophenol as the major metabolite, even in the presence of added GSH (Hissink et al. 1997b). Using cell lines expressing individual human cytochrome P-450 isozymes, it was revealed that CYP2E1, and not 1A1, 1A2, 2B6, 2C9, 2D6, 2A6, or 3A4, participated in 1,4-DCB metabolism.

Quantitative data on the elimination of 1,4-DCB in humans are not available. However, metabolites of 1,4-DCB have been detected in the urine of exposed humans (Ghittori et al. 1985; Hill et al. 1995; Pagnotto and Walkley 1965), demonstrating the urinary elimination of 1,4-DCB in humans. Animal studies of 1,4-DCB elimination have demonstrated that the compound is eliminated mainly in the urine, regardless of exposure route; elimination occurs in the form of metabolites, rather than as the parent compound.

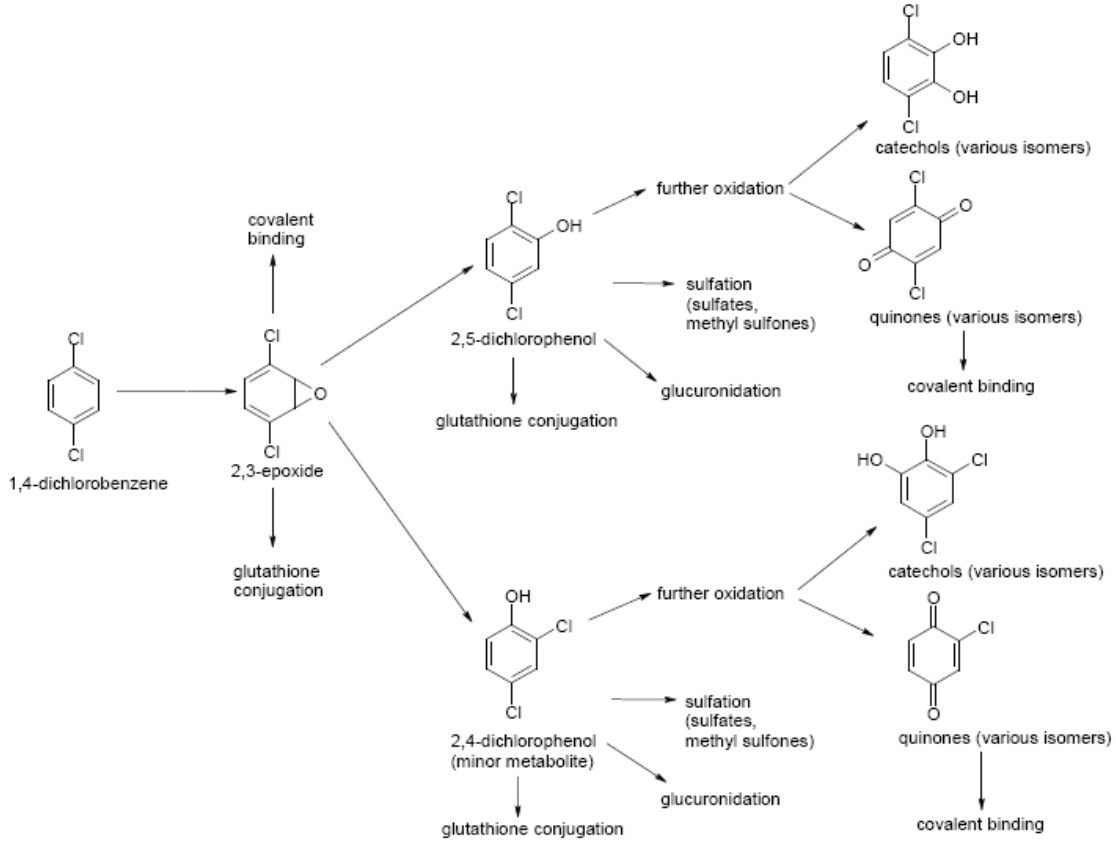


Figure 1 Predominant Metabolic Pathway for 1,4-DCB in Humans (USEPA 2006a)

Sections 4.2.2.3 and 4.2.4.1 contain additional information on the metabolism of 1,4-DCB as it relates to carcinogenicity. See ATSDR (2006), USEPA (2006a), or NICNAS (2000) for additional information regarding the metabolism of 1,4-DCB.

4.1.2.3Possible MOA for General Systemic Toxicity

While Section 3.1.2.2 discusses the MOA by which 1,4-DCB may produce the irritant effects relevant to the derivation of the acute ReV and ^{acute}ESL, this section focuses on the possible MOA relevant to other toxicological endpoints and derivation of the chronic ReV and $^{chronic}ESL_{threshold(nc)}$. Information regarding the possible MOA of 1,4-DCB-induced toxicity, primarily taken from ATSDR (2006) but not directly quoted, includes the following:

The hepatotoxicity and nephrotoxicity observed in laboratory animals are probably caused by the

formation of toxic intermediates formed during the conversion of 1,4-DCB to 2,5-dichlorophenol by cytochrome P-450, by depletion of glutathione-S-transferase (GSH) at higher doses of 1,4-DCB, or both. The data provide a strong indication that the mechanism behind the hepatic (and probably renal) toxicity of 1,4-DCB lies in the intermediate steps of metabolite formation and conjugation by cytochrome P-450. Formation of 2,5-dichlorophenol from 1,4-DCB via cytochrome P-450 metabolism likely produces some intracellular, intermediate metabolite(s) that are also hepatotoxic when sufficient amounts accumulate intracellularly. These yet unidentified metabolites are detoxified by GSH, but when GSH depletion occurs (e.g., likely to occur at higher oral doses), toxicity is enhanced. Hepatocytes respond to these insults by releasing intracellular enzymes, degeneration, vacuolation, necrosis, and increases in gross liver weight. However, these changes are not specific to 1,4-DCB and likely occur in a dose-responsive manner. At lower doses, cellular proliferation in the liver in the absence of these toxic-type responses has been observed; however, the mechanism behind this response needs to be more clearly defined. Exposure to 1,4-DCB likely follows similar metabolic pathways in the kidneys and would be responsible for the toxicity (e.g., increased organ weight, tubular degeneration, nephropathy) observed in that organ, and may also be associated with the formation of cancer-linked alpha-2μ-globulin in male rats. The microsomal mixed-function oxidase system and microsomal glutathione transferases, and to a lesser degree the cytosolic glutathione transferases, may also be involved in the bioactivation of 1,4-DCB.

With the exception of alpha-2μ-globulin in the male rat kidney, all detoxification pathways present in laboratory animal models are present in humans. Therefore, humans may be susceptible to the toxicity observed in laboratory animals.

4.1.3 Dose Metric

For the key studies, data on exposure concentration of the parent chemical are available. Since data on other more specific dose metrics (e.g., blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue) are not available for these studies, exposure concentration of the parent chemical will be used as the default dose metric (TCEQ 2012).

4.1.4 PODs for Key Studies

For the Aiso et al. (2005a) study, which has dichotomous data, TD performed benchmark dose (BMD) modeling using the dichotomous models in USEPA's BMD software (version 1.4.1c) to derive the study POD based on the increased incidence of nasal lesions (moderate or greater severity) in female rats. For the CPA (1986) key study, which has continuous data, TD performed BMD modeling using the continuous models in USEPA's BMD software (version 1.4.1c) to derive the study POD based on increased liver weight, more specifically, increased liver weight relative to brain weight in F_0 (parental) male rats. Appendices 1 and 2 contain detailed information whereas the following sections provide a summary of results.

4.1.4.1 Benchmark Response Level and Critical Effect Size

If there is an accepted level of change in an endpoint that is considered to be biologically adverse, then that amount of change is selected as the benchmark response (BMR) level for BMD modeling (USEPA 2000). For dichotomous data, the BMR is typically expressed as a specific percent increase in the incidence of an adverse outcome. For the Aiso et al. (2005a) study, a 10% increased incidence of nasal lesions compared to control incidence was considered an adverse response. This is consistent with ATSDR (2006), which did not consider this effect to be serious, as well as USEPA (2006a). The benchmark concentrations at the BMR_{10} (BMC_{10}) and the lower 95% confidence limit on the central estimate ($BMCL_{10}$) were calculated and are presented in Appendix 1.

To distinguish continuous data from dichotomous data, Dekkers et al. (2001) recommended the term "critical effect size" (CES) be used for continuous data instead of BMR since the effect measured is expressed on a continuous scale. A CES defines the demarcation between non-adverse and adverse changes in a toxicological effect parameter for continuous data (Dekkers et al. 2001). A 10% change in organ weight relative to the mean organ weight in the control animals (i.e., CES_{10}) is typically considered an adverse effect (USEPA 2000, Dekkers et al. 2001). Furthermore, this effect is considered to be mild per Table B-1 of TCEQ (2012). Therefore, for the CPA (1986) study, a BMC_{10} and $BMCL_{10}$ were calculated for the CES_{10} based on the critical effect of increased liver weight relative to brain weight. The BMC and BMCL with a CES of 1 standard deviation (SD) from the control mean (BMC_{1SD} and $BMCL_{1SD}$) were also calculated and are presented in Appendix 2 for comparison purposes, as suggested by USEPA (2000).

4.1.4.1.1 Benchmark Dose Modeling – Aiso et al. (2005a)

For derivation of the POD for the chronic inhalation MRL, ATSDR (2006) performed BMD modeling on the critical effect identified in Aiso et al. (2005a) (i.e., nasal lesions in female rats) using USEPA's Benchmark Dose software (version 1.3.2). More specifically, dichotomous model BMD analysis was conducted using the incidences of the nasal lesions (moderate or greater severity) in female rats. Other endpoints were not modeled by ATSDR because the effects occurred at higher concentrations (i.e., nasal lesions and hepatocellular hypertrophy in mice, kidney lesions in rats) or were not toxicologically significant (i.e., testicular mineralization in mice).

TD remodeled the data using USEPA BMD software (version 1.4.1c) and calculated the BMC_{10} and $BMCL_{10}$ based on extra risk above the control incidence (see Appendix 1). TD could not recreate ATSDR's modeling results for the log-probit model because it appears that ATSDR did not restrict the slope to ≥ 1 as indicted in footnote "c" to their Table A-5. It appears that this error resulted in ATSDR not being able to identify the log-probit as the model with the lowest Akaike's information criteria (AIC) value, and therefore the best fit. The table of BMD modeling results in Appendix 1 reports the correct values for the log-probit model as footnoted in Table A-5 of ATSDR (2006). Several models provided adequate fit to the data based on goodness-of-fit p

values > 0.1 and visual inspection of the dose-response curves with scaled residuals less than an absolute value of 2. The log-probit model was selected by TD (and USEPA 2006a) based on the lowest AIC value (i.e., best fit). TD selected a $BMCL_{10}$ as the POD, consistent with ATSDR (2006) and USEPA (2006a). The $BMCL_{10}$ for the log-probit model (14.9 ppm) is slightly lower than the study NOAEL (19.8 ppm), is similar to the $BMCL_{10}$ (9.51 ppm) selected by ATSDR (2006) as the POD for their chronic MRL, and was selected by TD for use as a potential POD for the chronic ReV and $^{chronic}ESL_{threshold(nc)}$.

TD also considered increased liver weight in mice as a potential critical effect since statistically significant increases were observed at 298.4 ppm, and the relative liver weight increase in mice was much greater than that for other organs (i.e., kidney weight increases in mice and rats, liver weight increases in rats). However, the BMD analyses (data not included in Appendix 1) showed that the potential POD values ($BMCL_{10}$ and $BMCL_{1SD}$) from continuous models with acceptable fits to the mouse liver weight data (i.e., power, polynomial, linear) were higher than the POD selected based on nasal lesions in female rats and would result in a higher POD_{HEC}.

4.1.4.1.2 Benchmark Dose Modeling – CPA (1986)

Increased liver weight in F_0 (parental) male rats was identified by TD and USEPA (1996) as the critical effect from CPA (1986). BMD analysis was conducted using USEPA BMD software (version 1.4.1c) based on male rat liver weight data and liver weight relative to brain weight data from Tables 18 and 20 of CPA (1986), respectively, which are given in Appendix 2. Expressing liver weight relative to brain weight is used to normalize liver weight for chemicals which may affect body weight, as was the case with high exposure to 1,4-DCB in the present study (especially for males). Therefore, BMD modeling results based on liver weight relative to brain weight data were used for identification of a POD. Goodness of fit was evaluated by p values > 0.1, visual inspection of the dose-response curves, and scaled residuals less than an absolute value of 2. The following models had an adequate fit: linear, polynomial, power, and Hill. The linear model gave a lower AIC value than the other models, indicating a better fit. The linear model produced a $BMCL_{10}$ value of 131.1 ppm, which was selected for use as a potential POD for the chronic ReV and $^{chronic}ESL_{threshold(nc)}$. This POD value based on liver weight normalized by brain weight in male rats is similar to the $BMCL_{10}$ from the linear model for increased liver weight in male rats without normalization by brain weight (125.1 ppm). See Appendix 2 for additional information.

TD also considered decreased weight gain in female rats on gestational day 20 as a potential critical effect since statistically significant decreases were observed at 211 and 538 ppm. However, the BMD analyses (data not included in Appendix 2) showed that the potential PODs from the continuous models with acceptable fits (i.e., power, polynomial, linear) were higher than the POD selected based on increased liver weight relative to brain weight in F_0 male rats.

4.1.5 Dosimetric Adjustments

4.1.5.1 Default Exposure Duration Adjustments

Because Aiso et al. (2005a) and CPA (1986) are discontinuous exposure animal studies, it is necessary to adjust the animal exposure regimen to a continuous exposure.

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

where: POD = POD from animal study based on discontinuous exposure regimen
D = exposure duration (hours per day)
F = exposure frequency (days per week)

Aiso et al. (2005a):
POD_{ADJ} = 14.9 ppm x (6/24) x (5/7) = 2.66 ppm

CPA (1986):
POD_{ADJ} = 131.1 ppm x (6/24) x (7/7) = 32.77 ppm

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

1,4-DCB is a Category 2 gas, being water soluble and capable of producing both point-of-entry and remote effects in the vapor phase. A Category 2 gas is treated as a Category 1 gas when deriving a health-protective air concentration based on a point-of-entry respiratory effect (e.g., irritation), and as a Category 3 gas when deriving a value based on a remote systemic effect (USEPA 1994, USEPA 2006a, USEPA 2012, TCEQ 2012).

4.1.5.2.1 Aiso et al. (2005a) study

The critical effect for the Aiso et al. (2005a) study is an increase in nasal lesions, which is a point-of-entry effect. Therefore, 1,4-DCB will be treated as a Category 1 gas with effects in the extrathoracic region for purposes of dosimetric adjustment from animals (i.e., rats) to humans (USEPA 1994, USEPA 2012). This is consistent with ATSDR (2006) for derivation of the chronic inhalation MRL and USEPA (2006a) for derivation of the draft RfC.

Dosimetric adjustments were performed as a Category 1 vapor based on updated recommendations on animal-to-human dosimetric adjustments in USEPA (2012): the default regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) is 1.

The default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$
$$= 2.66 \text{ ppm} \times 1$$
$$= 2.66 \text{ ppm}$$

4.1.5.2.2 CPA (1986) Study

The critical effect for the CPA (1986) study is an increase in liver weights of parental males, which is a systemic effect. Therefore, 1,4-DCB will be treated as a Category 3 gas. USEPA (2012) recommended that for category 3 gases, animal-to-human dosimetric adjustments be based on guidelines from USEPA (1994). For category 3 gases:

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

where: $H_{b/g}$ = ratio of the blood:gas partition coefficient
A = animal
H = human

Where the blood:gas partition coefficients for animals and humans are unknown, a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994).

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A/(H_{b/g})_H) = 32.77 \text{ ppm} \times 1 = 32.77 \text{ ppm}$$

4.1.6 Critical Effect and Adjustments of the POD_{HEC}

4.1.6.1 Critical Effect

Based on TCEQ (2012), the key study and critical effect with the lowest POD_{HEC} (e.g., the lowest adverse effect-based POD_{HEC}, as opposed to a NOAEL-based POD_{HEC}) is chosen to develop the ReV. The statistically significant increased incidence of nasal lesions in the olfactory epithelium of female rats (Aiso et al. 2005a) with a POD_{HEC} of 2.66 ppm is the critical effect because it is much lower than the POD_{HEC} based on statistically significant increased liver weight in F_0 (parental) male rats (i.e., POD_{HEC} of 32.77 ppm (CPA 1986)).

4.1.6.2 UFs

Section 4.1.2.3 discusses the MOA by which 1,4-DCB may produce toxicity, which is a threshold/nonlinear MOA. Therefore, UFs were applied to the POD_{HEC} value from the key study in deriving the chronic ReV. The POD_{HEC} of 2.66 ppm from Aiso et al. (2005a) was divided by an intrahuman variability UF of 10 (UF_H), an animal-to-human UF of 3 (UF_A), and a database UF of 1 (UF_D).

- A full UF_H of 10 was used to account for potentially sensitive subpopulations such as children, the elderly, those with pre-existing health conditions, and others since data regarding potential intrahuman sensitivity are lacking.A UF_A of 3 was used for potential pharmacodynamic differences between rats and humans since pharmacokinetic (dosimetric) adjustments from rats to humans were made.

- A UF_D of 1 was used because the chronic inhalation database for 1,4-DCB contains a variety of suitable studies (e.g., chronic inhalation, prenatal development, and two-generation reproductive toxicity studies) (USEPA 2006a) per TCEQ (2012),

- a LOAEL-to-NOAEL UF (UF_L) is not applicable as BMD modeling was performed, and the BMCL was used as the POD (TCEQ 2012).

Therefore, the total UF for Aiso et al. (2005a) is 30, consistent with ATSDR (2006) and USEPA (2006a).

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

As discussed in the previous section, UFs are applied to the POD_{HEC} of the key study (Aiso et al. 2005a) to derive the chronic ReV:

$$\begin{aligned} \text{chronic ReV} &= POD_{HEC} / (UF_H \times UF_A \times UF_D) \\ &= 2.66 \text{ ppm} / (10 \times 3 \times 1) \\ &= 0.0887 \text{ ppm} \\ &= 88.7 \text{ ppb} \end{aligned}$$

The chronic ReV value was rounded to two significant figures at the end of all calculations. Rounding to two significant figures, the chronic ReV for 1,4-DCB is 89 ppb (530 µg/m^3). The rounded chronic ReV was then multiplied by 0.3 to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 27 ppb (160 µg/m^3) (Table 5).

Table 5 Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameters	**Summary**
Study	Aiso et al. (2005a)
Study Population	150 exposed female rats (50 per exposure group), 50 controls
Study Quality	High
Exposure Levels	0, 19.8, 74.8, and 298.4 ppm (mean analytical concentrations)
Critical Effects	Increases in nasal olfactory epithelial lesions
BMC_{10}**23.37 ppm**POD ($BMCL_{10}$)	14.9 ppm
Exposure Duration	6 h per day, 5 days per week for 104 weeks
Extrapolation to continuous exposure (POD_{ADJ})	2.66 ppm (Category 1 vapor, $RGDR_{ET}$ = 1)
Extrapolation to humans (POD_{HEC})	2.66 ppm
Total UFs	30
Interspecies UF	*3*
Intraspecies UF	*10*
Incomplete Database UF *Database Quality*	*1* *High*
Chronic ReV (HQ = 1)	**530 µg/m^3 (89 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**160 µg/m^3 (27 ppb)**

4.1.8 Comparison of Results

The chronic ReV selected by the TD for 1,4-DCB (89 ppb) is somewhat higher than ATSDR's chronic inhalation MRL (30 ppb) (ATSDR 2006) and USEPA's draft RfC (13.3 ppb) (USEPA 2006a) because updated recommendations from USEPA (2012) for animal-to-human dosimetric adjustments were used.

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight-of-Evidence (WOE)

4.2.1.1 Other Agencies

IARC (1999) indicates that 1,4-DCB is possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals (i.e., mice, rats) by the oral route of exposure. Available studies in mice and rats exposed by inhalation were judged to be inadequate.

The US Department of Health and Human Services (DHHS) concluded that 1,4-DCB is reasonably anticipated to be a human carcinogen based on oral studies in rodents (NTP 2005). No adequate data were available to evaluate the carcinogenicity of 1,4-DCB in humans.

USEPA (1996) indicates that 1,4-DCB has not undergone a complete evaluation and determination under USEPA's IRIS program for evidence of human carcinogenic potential. However, the draft IRIS reassessment (USEPA 2006a) indicates that 1,4-DCB is considered “likely to be carcinogenic to humans” by both the inhalation and oral routes.

The Australian Department of Health and Ageing does not consider 1,4-DCB as carcinogenic (NICNAS 2000). Australia uses the same classification criteria as the European Union, and the European Commission Working Group on the Classification and Labeling of Dangerous Substances (ECWGCLDS) concluded in 1998 that 1,4-DCB-related carcinogenic events in animals are not relevant to humans. The Swedish National Institute for Working Life (NIWL), which documents the scientific basis for Swedish occupational standards, takes a less definite position than ECWGCLDS in regard to 1,4-DCB-induced mouse liver tumors, indicating that it is doubtful that these tumors are relevant to humans (NIWL 1998).

4.2.1.2 TCEQ Conclusions Regarding Calculation of a Carcinogenic-Based ESL

Carcinogenic WOE is a matter of scientific judgment which may differ among agencies and between routes of exposure (e.g., oral versus inhalation) in certain circumstances (e.g., lack of absorption, point-of-entry tumors). Based on inhalation exposure carcinogenicity data alone, it is not abundantly clear as to whether the “likely to be carcinogenic to humans” descriptor used for 1,4-DCB in USEPA (2006a) is justified under USEPA cancer guidelines (USEPA 2005). However, as carcinogenicity descriptors generally apply to all exposure routes in the absence of compelling information to the contrary (USEPA 2005), TD will treat 1,4-DCB as “likely to be carcinogenic to humans” in consideration of the oral carcinogenicity data. This designation is consistent with USEPA (2006a).

While TD will consider 1,4-DCB as likely to be carcinogenic to humans, currently available inhalation carcinogenicity data are deemed inadequate by TD for calculation of a carcinogenic-based ESL with an acceptable level of confidence, as discussed in Section 4.2.4. Therefore, a carcinogenic-based ESL will not be calculated at this time. This issue will be re-evaluated as new scientific studies become available. Currently available data and information that are relevant to

a carcinogenic assessment are discussed below.

4.2.2 Relevant Data

4.2.2.1 Human Data

No studies were located regarding cancer in humans after inhalation exposure to 1,4-DCB (ATSDR 2006).

4.2.2.2 Animal Data

ATSDR (2006) provides the following information on the carcinogenic potential of 1,4-DCB via inhalation in experimental animals:

No evidence of carcinogenicity was observed in a long-term inhalation study in rats that were exposed to 1,4-DCB at 75 or 500 ppm intermittently for 76 weeks (Riley et al. 1980a). The reported lack of extensive organ toxicity in this study (compared with results seen in oral studies described in Section 3.2.2.2) strongly suggests that a maximum tolerated dose (MTD) was not achieved. In addition, a less-than-lifetime dosing regimen was used. The experimental design limitations preclude reliable evaluation of potential inhalation carcinogenicity based on this study.

The carcinogenicity of 1,4-DCB was more recently evaluated in groups of 50 male and female F344/DuCrj rats, and 50 male and 50 female Crj:BDF1 mice, following exposure to concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b; Japan Bioassay Research Center 1995). Comprehensive histological evaluations (including nasal cavity, trachea, and lungs) showed no compound-related neoplastic changes in rats, although incidences of liver and lung tumors were elevated in mice. The liver tumors were induced in mice of both sexes, generally increased only at 300 ppm, and were comprised of several tumor types. Liver tumors reported to be significantly increased ($p \leq 0.05$, Fisher's Exact test) in male mice were hepatocellular carcinoma (12/49, 17/49, 16/50, 38/49; $p \leq 0.01$ at high dose), hepatoblastoma (0/49, 2/49, 0/50, 8/49; $p \leq 0.01$ at high dose) and hepatic histiocytic sarcoma (0/49, 3/49, 1/50, 6/49; $p \leq 0.05$ at high dose). Liver tumors reported to be significantly increased in female mice were hepatocellular carcinoma (2/50, 4/50, 2/49, 41/50; $p \leq 0.01$ at high dose), hepatocellular adenoma (2/50, 10/50, 6/49, 20/50; $p \leq 0.05$ at low and high doses), hepatocellular carcinoma or adenoma (4/50, 13/50, 7/49, 45/50; $p \leq 0.05$ at low and high doses), and hepatoblastoma (0/50, 0/50, 0/49, 6/50; $p \leq 0.05$ at high dose). Although the hepatocellular adenomas were increased in female mice at 20 and 300 ppm, the relevance of the increase at 20 ppm is unclear given the lack of significant change at 75 ppm. Lung bronchoalveolar adenoma and carcinoma were significantly increased in female mice (1/50, 4/50, 2/49, 7/50; $p \leq 0.05$ at high dose). Except for hepatoblastoma, all of the aforementioned liver and lung tumor incidences were reported to have a significant positive linear trend by the Peto test and/or Cochran-Armitage test.

However, Aiso et al. (2005a) indicates that the malignant lung tumor incidence reported for

female mice did not exceed the upper limit of historical control data, and they are not considered related to chemical exposure or relevant for quantitative cancer risk assessment (Butterworth et al. 2007). There was no increase in tumors (liver or lung) in rats, which is supported by negative results from rat liver tumor initiation/promotion assays (Gustafson et al. 1998, 2000).

4.2.2.3 Metabolism of 1,4-DCB Related to Carcinogenicity

The metabolism of 1,4-DCB is discussed in Section 4.1.2.2. The mouse liver more readily produces reactive metabolites such as chlorinated benzoquinone (e.g., 2,5-dichlorobenzoquinone) and benzohydroquinone (e.g., 2,5-dichlorohydroquinone) compared to the rat liver, and may result in greater 1,4-DCB-induced hepatotoxicity in mice as observed in a 13-week inhalation study (Aiso et al. 2005b). Consequently, the more severe hepatotoxicity observed in mice (e.g., necrosis, hepatocellular hypertrophy) may result in the greater liver tumor response in mice compared to rats (i.e., species differences), as cytotoxicity and regenerative cell proliferation are important mechanistic considerations for hepatocarcinogenesis (Aiso et al. 2005a).

Additional information regarding species differences in metabolism which may be related to species differences in hepatocarcinogenesis, taken from NICNAS (2000) although not directly quoted, is provided below.

Several lines of evidence suggest that species differences in the metabolism of 1,4-DCB by hepatic cytochrome P-450 may produce species differences in hepatotoxicity. A marked induction of CYP2B1/2 was observed in both the rat and mouse in response to 1,4-DCB exposure *in vivo* (Lake et al. 1997). Metabolism by CYP2B1/2 produces the 1,2-epoxide, with subsequent metabolism resulting in the formation of mono- and di-chlorohydroquinones (Klos and Dekant 1994). CYP2E1 is also involved in the metabolism of 1,4-DCB and results in the formation of the 2,3-epoxide, as opposed to the 1,2-epoxide resulting from CYP2B1/2 metabolism. Studies with human cell lines transfected with cDNA expressing specific cytochrome P450 isoforms revealed that only CYP2E1 participates in the human metabolism of 1,4-DCB (Hissink et al. 1997).

Substantial interspecies differences in the hepatic microsomal metabolism of 1,4-DCB have been demonstrated between mice, rats, and humans (Hissink et al. 1997). The rank order for hepatic microsomal metabolism was determined to be (as a percentage of total conversion): mice (16%) > rats (0.6% to 1.3%) > humans (0.3%). Covalent binding of 1,4-DCB metabolites to microsomal protein was demonstrated to have the following rank order (as a percentage of total conversion): mice (21%) > rats (10%) > humans (6%). The addition of ascorbic acid reduced microsomal covalent binding, indicating that benzoquinone species derived from hydroquinones, rather than epoxides, are primarily involved. The ascorbate-dependent reduction was 92% for mice compared to 25% for humans, from which it may be concluded that quinone/protein binding is not extensive for human microsomes**.** The addition of glutathione to microsomal preparations and analysis for glutathione-epoxide conjugates resulted in undetectable levels from mouse preparations, a 6% increase from human preparations, and a significant increase (range 40

to 52%) for all rat strains.

In mice, the metabolism of 1,4-DCB proceeds by the action of CYP2E1 and CYP2B1/2 with substantial hydroquinone formation, whereas in humans, metabolism proceeds by the action of CYP2E1 only with relatively minor formation of hydroquinones. As humans do not express CYP2B1/2, the 1,2-epoxide and subsequent hydroquinones are not produced in the human liver. Total hydroquinone formation (as a percentage of total hepatic microsomal metabolites and in the presence of ascorbate as reductant) was 8.86% for mice, while only 0.4% and 0.08% in rats and humans, respectively.

Thus, there are substantial differences in the hepatic metabolism of 1,4-DCB by mice in comparison to rats and humans (NICNAS 2000). Because hydroquinones have been implicated in murine hepatocarcinogenesis, these species differences in hepatic metabolism have implications for the relevance of mouse liver tumors to humans (see Section 4.2.4.1).

4.2.3 Carcinogenic MOA

This section contains information regarding possible MOAs discussed in the scientific literature for the murine hepatocarcinogenesis observed in oral gavage (NTP 1987) and inhalation (Aiso et al. 2005a) chronic studies.

4.2.3.1 Genotoxicity

1,4-DCB has not been shown to be mutagenic in microbial or mammalian systems (ATSDR 2006) and is not considered to have mutagenic potential *in vivo* or *in vitro* (WHO 1991, NICNAS 2000, NIWL 1998). The weight of evidence based on the large number of genotoxicity tests performed on 1,4-DCB strongly indicates that 1,4-DCB is unlikely to induce cancer via a DNA-reactive, mutagenic, or genotoxic MOA. Additionally, the shape of the dose-response curves for significantly elevated liver tumors in male and female mice in the Aiso et al. (2005a) study (no increased incidence at the two lowest exposure levels) strongly supports a nonlinear/threshold MOA for 1,4-DCB-induced liver tumors (Butterworth et al. 2007). *As available information strongly suggests that the liver tumors observed in mice are not the result of genotoxicity (see Section 4.2.1.1), researchers have focused on plausible nongenotoxic modes/mechanisms of action for murine hepatocarcinogenesis.*

4.2.3.2 Mitogenic MOA

Available data indicate that the mechanism leading to the formation of mouse liver tumors following 1,4-DCB exposure is sustained mitogenic stimulation and proliferation of hepatocytes, which may be a threshold response (USEPA 2006a). Butterworth et al. (2007) presents evidence that 1,4-DCB induces liver tumors via a mitogenic/promotional MOA. The stimulation of liver growth and a sustained increase in liver weight with continuous exposure are effects common to all mitogenic liver carcinogens (e.g., phenobarbital) and were clearly seen in the oral gavage and inhalation cancer bioassays. Mitogens provide a selective growth advantage (i.e., promotion) to precancerous lesions, whether spontaneous or chemically-induced. The study authors indicate

that the evidence (e.g., increased liver weight during exposure, increased number of S-phase cells, mitotic cell proliferation as opposed to regenerative, large liver weight increases preceding tumor induction, dose-dependent liver weight increases in parallel/directly proportional to liver tumor induction) constitutes a cohesive and classical pattern of activity for chemicals acting via a nongenotoxic-mitogenic/promotional MOA. This MOA would predict a nonlinear threshold dose-response relationship, with no excess tumors at exposure concentrations that are insufficient to cause mitogenic/promotional activity and resulting sustained increases in liver weight. There is evidence from a rat initiation-promotion study that the MOA for 1,4-DCB has a threshold, and evidence of nonlinearity and a threshold for increased liver weight and tumor induction based on the Aiso et al. (2005a) data (Butterworth et al. 2007). However, USEPA (2006a) indicates that available evidence is not yet sufficient to warrant a nonlinear MOA. Additional information on a possible carcinogenic MOA is provided in Section 4.2.4.3.

4.2.4 Justification for Not Developing a Carcinogenic-Based ESL

As inhalation is the principal route of human exposure to 1,4-DCB, carcinogenicity data from inhalation animal studies are more relevant for human health risk assessment than those from oral animal studies. Only a single animal study was located which shows an increased incidence of cancer with 1,4-DCB inhalation exposure (cited as Aiso et al. 2005a in this document; see Section 4.2.2.2), and there are no human studies which demonstrate or suggest that the carcinogenic potential (i.e., liver tumors) shown in Aiso et al. (2005a) has resulted in human tumors. In fact, no human cancer studies on 1,4-DCB inhalation exposure were located (ATSDR 2006). In Aiso et al. (2005a), a statistically significant increase in cancer occurred only in mice (not rats), and only at the highest exposure concentration of 298.3 ppm.

While the TCEQ Toxicity Factors Guidelines (TCEQ 2012) indicate that the TD generally performs carcinogenic dose-response assessments for chemicals considered “carcinogenic to humans” or “likely to be carcinogenic to humans” under the USEPA Cancer Guidelines (USEPA 2005), animal inhalation cancer data are considered by TD to be inadequate at this time for calculation of a carcinogenic-based ESL with an acceptable level of confidence. Significantly increased cancer was observed in only one inhalation study (Aiso et al. 2005a), in one species (BDF_1 mice), and only at the highest dose (298.3 ppm). There are issues related to:

1. significant differences in 1,4-DCB metabolism between mice and humans which have caused some agencies (e.g., ECWGCLDS, NIWL) to conclude that mouse liver tumors are irrelevant or likely irrelevant to humans (Section 4.2.4.1);
2. the shape of the dose-response curve and whether linear low-dose extrapolation is appropriate based on the carcinogenic MOA analysis (Section 4.2.4.2);
3. increased cancer only being observed at the maximum tolerated dose (MTD) in Aiso et al. (2005a) and whether the carcinogenic MOA operative at the MTD is relevant to environmental exposure levels (Section 4.2.4.3); and
4. whether dosimetric differences preclude route-to-route extrapolation based on oral gavage data from the National Toxicology Program (NTP 1987) (Section 4.2.4.4).

Additionally, another chronic inhalation cancer study confirming the positive results reported in Aiso et al. (2005a) in laboratory animals is lacking, although another long-term inhalation study in rats (which had some limitations) showed no evidence of carcinogenicity (Riley et al. 1980), and there are no human data which suggest that the carcinogenic potential demonstrated in mice has resulted in tumors in humans.

4.2.4.1 Relevance of Mouse Liver Tumors to Humans

Differences between mice and humans in 1,4-DCB metabolism (Section 4.2.2.3) raise questions regarding the relevance of mouse liver tumors to humans. More specifically, hydroquinones have been implicated in murine hepatocarcinogenesis, and there are species differences in the production of hydroquinones during 1,4-DCB metabolism. It has been established that the metabolism of 1,4-DCB in mice results in substantial hydroquinone formation, whereas in humans, metabolism produces relatively minor amounts of hydroquinones. As humans do not express CYP2B1/2, the 1,2-epoxide and subsequent hydroquinones are not produced in the human liver (NICNAS 2000).

In 1998, ECWGCLDS concluded that 1,4-DCB-related carcinogenic events in animals are not relevant to humans. The ECWGCLDS considered the mouse liver tumors and rat kidney tumors induced by 1,4-DCB to be species-specific (e.g., related to alpha-2µ-globulin-mediated nephropathy in rats, and substantial 1,2-epoxide and subsequent hydroquinone formation by mice) and irrelevant to humans (NICNAS 2000). Alpha-2µ-globulin-mediated nephropathy and carcinogenesis in male rats has been generally adopted by the scientific community as not predictive of human carcinogenic risk. Although no specific mode/mechanism or metabolite(s) has gained widespread acceptance by the scientific community as being the causative factor in 1,4-DCB-induced mouse liver carcinogenesis, evidence suggests that the substantial production of hydroquinones in mice plays a causative role, and the modulation of cellular function by hydroquinone species provides a plausible mechanism for the increased numbers of mouse liver tumors following long-term exposure to 1,4-DCB (NICNAS 2000).

4.2.4.2 Dose-Response Curve and Linear Low-Dose Extrapolation

The cancer guidelines (USEPA 2005) recommend use of at least three dose groups to provide an indication of the shape of the dose-response curve. In Aiso et al. (2005a), however, statistically increased cancer incidence was not demonstrated at the two lower exposure levels (19.9 and 74.8 ppm), so information on the shape of the dose-response curve between the highest (298.3 ppm) and second highest (74.8 ppm) exposure concentrations is lacking. Characterization of the shape of the dose-response curve by appropriate low and middle dose selection is important in providing relevant dose-response data for assessing human risk (USEPA 2005). Furthermore, linear low-dose extrapolation based on the high tumor incidence in the 298.3 ppm exposure group in Aiso et al. (2005a) appears not to be appropriate based on available evidence which supports the proposed nongenotoxic-mitogenic MOA for murine hepatocarcinogenesis (see Section 4.2.3.2). In fact, overall comments from the External Peer Review Panel for the current draft of the USEPA IRIS risk assessment document for 1,4-DCB indicate that use of linear low-

dose extrapolation for the inhalation cancer study data appears not to be justified (USEPA 2006b, Butterworth et al. 2007). TD notes that there is evidence from a rat initiation-promotion study that the MOA for 1,4-DCB has a threshold, evidence of nonlinearity and a threshold for increased liver weight and tumor induction based on the Aiso et al. (2005a) data, and that some researchers consider a nonlinear threshold approach as most appropriate based on currently available data (Butterworth et al. 2007).

4.2.4.3 Carcinogenic MOA at the MTD

The highest dose in Aiso et al. (2005a) was the rodent MTD as determined from the 13-week study of Aiso et al. (2005b). It appears that the highest dose used in Aiso et al. (2005a) was an adequate estimate of the MTD in the most sensitive species as male mice had a significantly reduced body weight of 12% compared to controls and females had an approximately 9% decrease (although not statistically significant). Several authors have suggested that exposure to high doses such as the MTD may cause cytotoxicity, leading to increased carcinogenicity due to an increased opportunity for cancerous mutations to arise during regenerative cell proliferation (Gaylor 2005).

Based on the results of a fairly recent review of 156 NTP chronic bioassays, 62% of the chemicals tested showed evidence of carcinogenicity at the MTD, including non-genotoxic chemicals such as 1,4-DCB (Gaylor 2005). Statistical analyses conducted by Gaylor (2005) indicate that it appears almost all chemicals would be carcinogenic at the MTD if tested in an adequate number of animals (e.g., 200 per group). The study author suggests that it can be assumed that all chemicals may cause cancer at the MTD, which does not imply that most chemicals cause cancer at much lower, environmentally-relevant exposure levels. Because the highest dose in Aiso et al. (2005a) was the MTD, the conclusions of Gaylor (2005) suggest that the carcinogenic response in the highest dose group may have been due to a universal MOA operative at high doses (e.g., cytotoxicity-induced regenerative cell proliferation) rather than an MOA specific to 1,4-DCB which would be operative at much lower concentrations.

4.2.4.4 Dosimetric Differences in Route-to-Route Extrapolation

In regard to potential route-to-route extrapolation (oral-to-inhalation), there may be important route differences in dosimetry between the available oral gavage carcinogenicity study (NTP 1987) and inhalation exposure. The reported gastrointestinal absorption of 1,4-DCB in mice (71%) is greater than that for lung absorption (59%). Most importantly, oral administration by gavage is considered to rapidly increase blood and organ (e.g., liver) 1,4-DCB levels and have a first-pass effect, possibly causing more severe target organ toxicity/carcinogenicity than an inhalation exposure resulting in an equivalent intake over a longer duration (Aiso et al. 2005a, 2005b). An example may be the hepatocellular cytolethality and necrosis observed in the oral gavage study but not in the inhalation study (Butterworth et al. 2007). TD *believes that this route difference in internal dosimetry/dose rate and its potential effect on carcinogenesis cannot be appropriately adjusted for (e.g., there is no physiologically-based pharmacokinetic (PBPK) model for 1,4-DCB) and precludes route-to-route extrapolation based on the available oral*

carcinogenicity study (NTP 1987, TCEQ 2012).

Additionally, USEPA (2005) indicates that overt toxicity or qualitatively altered toxicokinetics due to excessively high doses may result in tumor effects that are secondary and not directly attributable to the chemical, that the results of studies utilizing excessively high doses may not be considered suitable for dose-response extrapolation, and that a sign of treatment-related toxicity associated with excessively high dose may include marked changes in organ weight, morphology, and histopathology. Both doses used in the oral gavage study that induced tumor increases (both sexes of $B6C3F_1$ mice) also produced these marked changes as evidenced by the induction of liver enlargement, substantial hepatotoxicity, and hepatocellular degeneration, cell size alterations, and focal necrosis in both sexes of mice and more than two-thirds of male mice even at the low dose (Butterworth et al. 2007). In regard to altered toxicokinetics, the extremely high dose rate associated with oral gavage can substantially alter the toxicokinetic profile within the animal and overwhelm defense mechanisms that would have been protective if the same dose had been absorbed over a longer duration such as with chronic inhalation exposure (Butterworth et al. 2007). Therefore, in addition to the usual difficulties and concerns associated with route-to-route extrapolation, the oral gavage study may have utilized doses that resulted in overt toxicity and qualitatively altered toxicokinetics, inducing tumor formation secondary to toxicity rather than directly attributable to the chemical. This casts further doubt on the scientific defensibility of using the oral data for inhalation quantitative risk assessment.

Despite serious TD reservations about route-to-route extrapolation of the oral gavage results, it is noted that 100 ppb was the most conservative cancer-protective air concentration derived for humans in a recent BMD analysis of male mouse liver cancer (most sensitive gender) based on the oral (NTP 1987) and inhalation (Aiso et al. 2005a) datasets combined on an absorbed dose basis ($BMDL_{01}$ with a total UF of 300) (Butterworth et al. 2007). This concentration is higher than the chronic ReV of 89 ppb and ${}^{chronic}ESL_{threshold(nc)}$ of 27 ppb based on noncarcinogenic effects.

If one were to assume that the proposed nongenotoxic-mitogenic MOA for murine hepatocarcinogenesis is valid and a nonlinear/threshold effect, this comparison suggests that protection against the noncarcinogenic effects of 1,4-DCB is also protective of carcinogenic effects.

4.3 Welfare-Based Chronic ESL

No data were found on the potential effects of 1,4-DCB on vegetation.

4.4 Long-Term ReV and ESL

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

- chronic ReV = 530 µg/m^3 (89 ppb)
- ${}^{chronic}ESL_{threshold(nc)}$ = 160 µg/m^3 (27 ppb)

The chronic ReV for 1,4-DCB is 530 µg/m^3 (89 ppb). At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 160 µg/m^3 (27 ppb) which will be used for the evaluation of air permits (Table 2).

4.5 Chronic Inhalation Observed Adverse Effect Level

The BMC_{10} from the Aiso et al. (2005a) of 23.37 ppm (Table 5) was used as the POD for calculation of a chronic inhalation observed adverse effect level. No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to calculate a $BMC_{10\ HEC}$:

The $BMC_{10\ HEC}$ was calculated using the following equation:

$$\begin{aligned} BMC_{10\ HEC} &= BMC_{10} \times RGDR_{ET} \text{ (Section 4.1.5.2)} \\ &= 23.37 \text{ ppm} \times 1 \\ &= 23.37 \text{ ppm} \\ &= 23{,}000 \text{ ppb (rounded to two significant figures)} \end{aligned}$$

The $BMC_{10\ HEC}$ determined from an animal study, where effects occurred in some animals, 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 or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 140,000 µg/m^3 (23,000 ppb) is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the chronic inhalation observed adverse effect level of 23,000 ppb to the ReV of 89 ppb is a factor of approximately 260.

Chapter 5 References

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Appendix 1: Benchmark Dose Modeling Results for Aiso et al. (2005a)

ATSDR (2006) performed BMD modeling on the critical effect identified in Aiso et al. (2005a) (i.e., nasal lesions in female rats) using USEPA's BMD software (version 1.3.2) for derivation of the POD for the chronic inhalation MRL. More specifically, dichotomous model BMD analysis was conducted using the incidences of the nasal lesions (moderate or greater severity) in female rats. Using benchmark response lower 95% confidence limit levels of 10% ($BMCL_{10}$) extra risk above the control incidence, TD remodeled the data using more recent USEPA BMD software (version 1.4.1c). TD could not recreate ATSDR's modeling results for the log-probit model because it appears that ATSDR did not restrict the slope to ≥ 1 as indicted in footnote "c" to their Table A-5. It appears that this error resulted in ATSDR not being able to identify the log-probit as the model with the lowest Akaike's information criteria (AIC) value, and therefore the best fit. The table of BMD modeling results below reports the correct values for the log-probit model as footnoted in Table A-5 of ATSDR (2006). Several models provided adequate fit to the data based on goodness-of-fit p values > 0.1 and visual inspection with scaled residuals less than an absolute value of 2. The log-probit model was selected by TD based on the lowest AIC value (i.e., best fit). Like ATSDR (2006), TD selected a $BMCL_{10}$ as the POD (the critical effect was not considered serious by ATSDR). The $BMCL_{10}$ for the log-probit model (14.9 ppm) is slightly lower than the study NOAEL (19.8 ppm) and is similar to the $BMCL_{10}$ (9.51 ppm) selected by ATSDR (2006) as the POD for their chronic MRL.

Aiso et al. (2005a) Modeled Data

Dose Group (ppm)	Number of Female Rats in Dose Group	Number of Female Rats with Nasal Olfactory Epithelial Lesions [a]	Incidence
0	50	27	0.54
19.8	50	29	0.58
74.8	50	39 [b]	0.78
298.4	50	47 [b]	0.94

[a] Moderate or greater severity from Table 3 of Aiso et al. (2005a).
[b] Significantly different than controls (p ≤ 0.05) per ATSDR (2006).

(see next page for modeling results)

BMC Modeling Results Based on Aiso et al. (2005a)

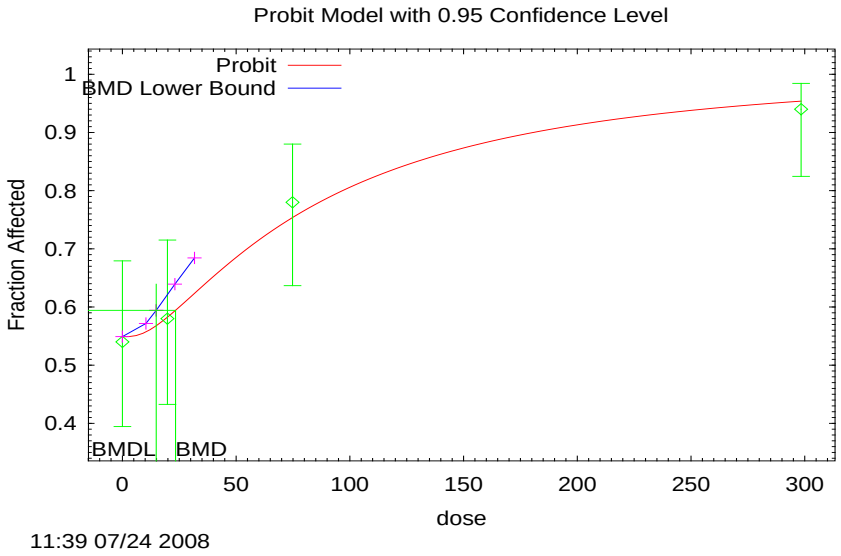
Dichotomous Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	Goodness-of-Fit p value [a]	AIC Value [b]
gamma [c]	14.0846	9.5136	0.7015	217.128
logistic	19.4316	13.8955	0.5101	217.786
log-logistic [e]	15.4509	4.1158	0.7445	218.517
multistage [d]	14.0846	9.5136	0.7015	217.128
probit	22.1727	16.7064	0.4182	218.211
log-probit [e]	23.3660	**14.8644**	0.8110	216.818
quantal linear	14.0846	9.5136	0.7015	217.128
weibull [c]	14.0846	9.5136	0.7015	217.128

[a] p value > 0.1 indicates adequate fit.
[b] lower AIC values generally indicate better fit.
[c] power restricted ≥ 1
[d] betas restricted ≥ 1, degree of polynomial = 2
[e] slope restricted ≥ 1

Benchmark Dose Computation: **Log-Probit Model for Nasal Lesions in Female Rats**

Specified effect =0.1
Risk Type = extra risk
Confidence level = 0.95

BMD = 23.366 ppm
BMDL = 14.8644 ppm



Appendix 2: BMD Modeling Results for CPA (1986)

Increased liver weight in male rats is the critical effect identified from CPA (1986). BMD analysis was conducted using USEPA BMD software (version 1.4.1c) based on male rat liver weight data and liver weight relative to brain weight data from Tables 18 and 20 of CPA (1986), respectively. Expressing liver weight relative to brain weight is used to normalize liver weight for chemicals which may affect body weight, as was the case with high exposure to 1,4-DCB in the present study. Therefore, BMD modeling results based on liver weight relative to brain weight data were used for identification of a POD. Goodness of fit was evaluated by p values > 0.1, visual inspection, and scaled residuals less than an absolute value of 2. Several models had an adequate fit. The linear model gave a lower Akaike's information criteria (AIC) value than other models, indicating a better fit. The linear model produced a $BMCL_{10}$ of 131.1 ppm, which was selected for use as the POD for the chronic ReV/ESL (see first set of BMD results below). This POD value based on liver weight normalized by brain weight in male rats is similar to the $BMCL_{10}$ from the linear model for increased liver weight in male rats without normalization by brain weight (125.1 ppm) (see second set of BMD results below). The linear model dose-response curve for the POD is shown below as plotted by the USEPA BMD software.

CPA (1986) Modeled Liver Relative to Brain Weight Data

Dose Group (ppm)	Liver Relative to Brain Weight (g)	SD	Number of Subjects
0	936.901	116.1747	27
66.3	1013.791	140.0916	28
211	1107.892 [a]	115.3417	28
538	1284.09 [a]	144.1823	28

[a] Significantly different than controls ($p < 0.01$).

BMC Liver Relative to Brain Weight Modeling Results Based on CPA (1986)

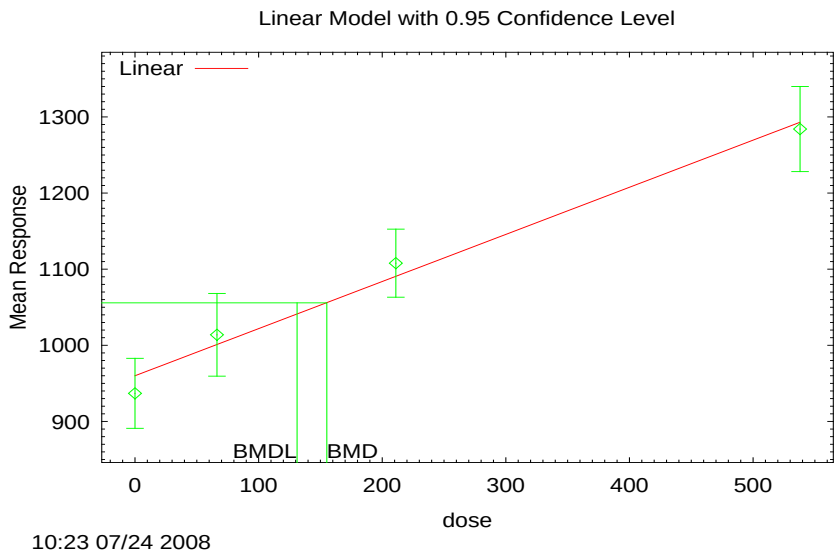
Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	1 SD BMC (ppm)	1 SD BMCL (ppm)	Goodness-of-Fit p value [a]	AIC Value [b]
linear	155.16	**131.10**	207.62	174.19	0.4054	1194.89
polynomial	110.64	74.32	153.55	105.72	0.5457	1195.45
power [c]	92.554	39.345	139.95	73.665	0.8693	1195.11
Hill	105.33	60.83	148.44	91.34	0.5976	1195.37

[a] p value > 0.1 indicates adequate fit.
[b] lower AIC values generally indicate better fit.
[c] power not restricted

Benchmark Dose Computation: Linear Model for Increased Liver Relative to Brain Weight in Male Rats

Specified effect =0.1
Risk Type = relative risk
Confidence level = 0.95

BMD = 155.161 ppm
BMDL = 131.102 ppm



CPA (1986) Modeled Liver Weight Data

Dose Group (ppm)	Liver Weight (g)	SD	Number of Subjects
0	20.545	2.2392	27
66.3	21.703	2.8927	28
211	23.799 [a]	2.5195	28
538	28.269 [a]	2.958	28

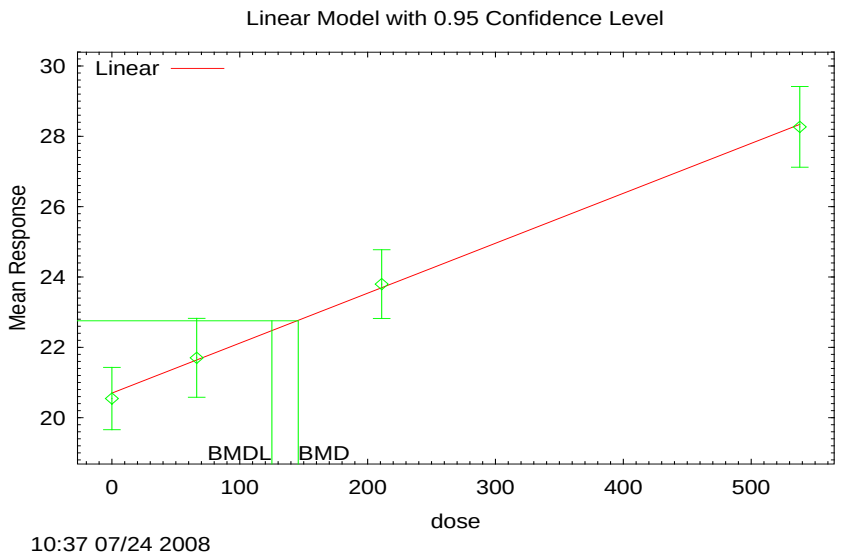
[a] Significantly different than controls ($p < 0.01$).

BMC Liver Weight Modeling Results Based on CPA (1986)

Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	1 SD BMC (ppm)	1 SD BMCL (ppm)	Goodness-of-Fit p value [a]	AIC Value [b]
linear	145.73	125.12	184.95	156.95	0.9187	331.28
polynomial	131.67	86.96	169.18	115.47	0.8672	333.14
power [c]	127.66	66.15	166.48	98.877	0.9509	333.12
Hill	131.24	81.15	168.81	110.14	0.8719	333.14

[a] p value > 0.1 indicates adequate fit.
[b] lower AIC values generally indicate better fit.
[c] power not restricted

Benchmark Dose Computation: Linear Model for Increased Liver Weight in Male Rats

Specified effect =0.1
Risk Type = relative risk
Confidence level = 0.95

BMD = 145.727 ppm
BMDL = 125.124 ppm