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Ethylbenzene

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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List of Acronyms and Abbreviations

Abbreviation	Definition
ACGIH	American Congress Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AIHA	American Industrial Hygiene Association
AMCV	Air monitoring comparison values
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
BTEX	Benzene, toluene, ethylbenzene, xylene
^{0}C	Celsius degrees
C	Concentration or Celsius
Cal EPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CNS	Central Nervous System
d	Day or days
D	Exposure duration, hours per day
DNA	Deoxyribonucleic acid
DSD	Development support document
E	Exposure level or concentration
ESL	Effects Screening Level
^{acute}ESL	Acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	Acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	Acute vegetation-based Effects Screening Level
$^{chronic}ESL_{linear(c)}$	Chronic health-based Effects Screening Level for linear dose response cancer effect
$^{chronic}ESL_{linear(nc)}$	Chronic health-based Effects Screening Level for linear dose response noncancer effects
$^{chronic}ESL_{nonlinear(c)}$	Chronic health-based Effects Screening Level for nonlinear dose response cancer effects
$^{chronic}ESL_{nonlinear(nc)}$	Chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
$^{chronic}ESL_{veg}$	Chronic vegetation-based Effects Screening Level

Abbreviation	Definition
F	Exposure frequency, days per week
h	Hour
$(H_{b/g})_A$	Blood gas partition coefficient for animal
$(H_{b/g})_H$	Blood gas partition coefficient for human
HEC	Human equivalent concentration
Hg	Mercury
HQ	Hazard quotient
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
K	Constant level or severity of response
Kow	Octanol water partition coefficient
LOAEL	Lowest-observed-adverse-effect-level
m	Meter
MAK	Maximale Arbeitsplatz Konzentration
mm	Millimeter
mg	Milligram
mg/L	Milligram per liter
MW	Molecular weight
µg	Microgram
$\mu g/m^3$	Microgram per cubic meter
min	Minute
MOA	Mode of action
MRL	Minimal Risk Level
MTD	Maximum tolerated dose
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effect-level
NRC	National Research Council
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment
OHC	Outer hair cell
OSHA	Occupational Safety and Health Administration

Abbreviation	Definition
POD	Point of departure
POD_{ADJ}	Point of departure adjusted for exposure duration
POD_{HEC}	Point of departure adjusted for human equivalent concentration
ppb	Parts per billion
ppm	Parts per million
ReV	Reference Value
RfC	Reference Concentration
T	Time or exposure duration
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
WOE	Weight of evidence

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 evaluation of acute and chronic ethylbenzene exposure. Please refer to the Air Monitoring Comparison Value Document (AMCV Document) available at AMCVs at TCEQ for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information of chemical and physical data for ethylbenzene.

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

Short-Term Values	Concentration	Notes
acute ReV	86,000 µg/m^3 (20,000 ppb) **Short-Term Health**	**Critical Effect(s):** ototoxicity in rats
$^{acute}ESL_{odor}$	--- **Short-Term Odor**	Aromatic odor
$^{acute}ESL_{veg}$	--- **Short-Term Vegetation**	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	1,900 µg/m^3 (450 ppb) **Long-Term Health**	**Critical Effect:** renal toxicity in rats
$^{chronic}ESL_{linear(c)}$	---	Insufficient data
$^{chronic}ESL_{veg}$	--- **Long-Term Vegetation**	No data found

Abbreviations used in Tables 1 and 2: **HQ**, hazard quotient; **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **AMCV**, air monitoring comparison value; **ESL**, Effects Screening Level; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL $_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL

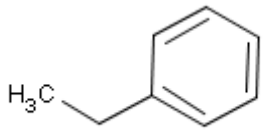
Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	26,000 µg/m^3 (6,000 ppb) [a] **Short-Term ESL for Air Permit Reviews**	Critical Effect(s): ototoxicity in rats
$^{acute}ESL_{odor}$	---	Aromatic odor
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	570 µg/m^3 (135 ppb) [b] **Long-Term ESL for Air Permit Reviews**	Critical Effect: renal toxicity in rats
$^{chronic}ESL_{linear(c)}$	---	Insufficient data
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 86,000 µg/m^3 (20,000 ppb) (Table 1) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 1,900 µg/m^3 (450 ppb) (Table 1) 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_8H_{10}	Hazardous Substances Data Bank (HSDB 2000)
Chemical Structure		Chemfinder (2004)
Molecular Weight	106.16	HSDB (2000)
Physical State	Liquid	HSDB (2000)
Color	Colorless	HSDB (2000)
Odor	Aromatic	HSDB (2000)
CAS Registry Number	100-41-4	HSDB (2000)
Synonyms	EB; Ethyl Benzene; Ethylbenzol; Phenylethane	HSDB (2000)
Solubility in water, mg/L	169 at 25°C	HSDB (2000)
Log K_{ow}	3.15	HSDB (2000)
Vapor Pressure	9.6 mm Hg at 25°C	HSDB (2000)
Relative Vapor Density	3.66	HSDB (2000)
Density	0.867 at 20°C	HSDB (2000)
Melting Point	-94.9°C	HSDB (2000)
Boiling Point	136.1 °C	HSDB (2000)
Conversion Factors	1 μg/m^3 = 0.23 ppb 1 ppb = 4.30 μg/m^3	Toxicology Division

Chapter 2 Major Uses or Sources

Ethylbenzene is 1 of 4 aromatic solvents collectively referred to as BTEX (i.e., benzene, toluene, ethylbenzene, and xylene). All 4 solvents are commonly used components of gasoline and fuel oil. Ethylbenzene's primary use is as a chemical intermediate in the production of styrene. It is also used as a solvent by itself, and in the production of organic compounds other than styrene. Ethylbenzene occurs naturally in petroleum products, and is a common constituent of automobile and aviation fuels. Since ethylbenzene is a component of petroleum products, it is also a byproduct of their combustion (HSDB 2000).

Ethylbenzene is emitted into the environment through the use of fuels, solvents, and by manufacturing processes. Upon its release into ambient air, ethylbenzene exists as a vapor. Ethylbenzene may also volatilize into ambient air from soil, sediment, and groundwater (HSDB 2000). An additional source of ethylbenzene exposure can be attributed to inhaling cigarette smoke (Polzin et al. 2007). Similar to other BTEX solvents, inhalation is the primary route of ethylbenzene exposure for the general public.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Study

Ethylbenzene is a colorless liquid with a gasoline-like odor, and readily evaporates into ambient air at room temperature. Once in the air, ethylbenzene is degraded by reacting with photochemically-produced hydroxyl radicals, and the reaction's half-life is estimated to be 55 hours (HSDB 2000). Considering ethylbenzene's physiochemical characteristics, and its behavior in the environment, inhalation is the primary route for human exposure. Its chemical and physical properties are summarized in Table 3.

The Toxicology Division (TD) conducted a thorough search of the scientific literature concerning the toxicity of ethylbenzene. Because of time and resource constraints, our evaluation of ethylbenzene toxicity is primarily based on background readings from the draft ATSDR (2007) toxicological profile. However, the TD obtained copies of key studies and supporting studies and critically reviewed these studies.

The ethylbenzene inhalation exposure database is extensive. Ethylbenzene's acute toxicity is similar to that of other aromatic solvents (i.e., toluene, xylene and styrene) with the central nervous system (CNS) as the primary target organ. Although Yant et al. (1930) reported eye and throat irritation in human volunteers after acute inhalation exposure to high concentrations of ethylbenzene, even higher concentrations produced CNS effects (i.e., vertigo and dizziness) in the same volunteers. An occupational inhalation exposure study at relatively low concentrations of solvent mixtures, including ethylbenzene, reported CNS effects (i.e., hearing loss) among workers (Sliwinska-Kowalska et al. 2001). Although human exposure data are preferable, many human inhalation exposure studies including the Sliwinska-Kowalska et al. (2001) study do not clearly characterize ethylbenzene exposure.

Because of the unclear ethylbenzene exposure characterizations in human inhalation studies, consideration was given to several well-conducted acute inhalation studies in rodents reporting adverse effects of the CNS, in particular the auditory system. Auditory system effects (e.g., auditory threshold deterioration and altered cochlear morphology) occurred in rats after acute-duration inhalation exposures that ranged between 300 ppm and 800 ppm ethylbenzene (Cappaert et al. 1999, 2000, 2001, 2002). Considering that hearing loss in workers was reported

by Sliwinska-Kowalska et al. (2001), the rat appears to be an appropriate animal model, and the auditory system appears to be the critical endpoint for ethylbenzene acute toxicity.

In the Cappaert et al. (2000) study, 32 Wag/Rij rats (8 rats per group) were exposed to 0, 300, 400, or 550 ppm ethylbenzene for 8 hours (h) per day for 5 consecutive days in an inhalation chamber. Between 3 to 6 weeks after the last ethylbenzene exposure, auditory function tests were performed by measuring compound action potentials, and distortion product otoacoustic emissions. In addition, outer hair cell (OHC) loss was quantified by histological examination. At 400 and 550 ppm ethylbenzene, increased auditory thresholds and OHC losses were observed. The 300 ppm ethylbenzene exposure group was identified as the No-Observed-Adverse-Effect-Level (NOAEL) for auditory effects. The 400 ppm ethylbenzene exposure group is the Lowest-Observed-Adverse-Effects-Level (LOAEL). Therefore, the point of departure (POD) is the NOAEL of 300 ppm. Cappaert et al. (2000) was selected as the key study over other acute exposure animal studies, because it is a recent well conducted study, it was chosen by ATSDR (2007) in its development of an acute minimal risk level (MRL), and it clearly identifies the NOAEL of 300 ppm for auditory system effects.

The following inhalation studies in rodents add to the weight of evidence (WOE) supporting ethylbenzene as a potent ototoxic agent:

- Gagnaire et al. (2007) reported moderate to severe ototoxicity in rats exposed to 200, 400, 600, and 800 ppm ethylbenzene by inhalation, 6 h/day, 6 days/week for 13 weeks. Increased auditory thresholds and moderate to severe losses of OHC of the organ of Corti (located in the cochlea) were observed. Auditory thresholds were unaffected at the lowest dose group, although 4 of 8 rats exposed to 200 ppm ethylbenzene showed insignificant OHC losses. For this reason, a NOAEL was uncertain. This 13 week study supports ototoxicity as the critical effect, and suggets that exposure duration may play a role in its ototoxicity.
- Cappaert et al. (2002) concluded that an inhalation exposure of 550 ppm ethylbenzene in rats for 8 h/day for 5 days resulted in deteriorated auditory thresholds, and OHC losses in the corresponding cochlear regions. In contrast, guinea pigs similarly exposed to 2,500 ppm ethylbenzene showed no auditory threshold shifts or OHC losses. Ethylbenzene concentration in blood was determined for both species after inhalation exposure to 500 ppm ethylbenzene, 8 h/day for 3 days. The ethylbenzene concentration in rat blood was 4.3 times higher than in guinea pig blood. Apparently, the difference in species sensitivity may be related to the amount of ethylbenzene in the blood.
- Cappaert et al. (2001) reported ototoxic effects after simultaneous exposure to ethylbenzene and to broad-band noise in rats. Inhalation exposures consisted of 0, 300 and 400 ppm ethylbenzene, and three noise levels (including background noise) and all their combinations, 8 h/day for 5 days. OHC loss was reported at both ethylbenzene exposure concentrations. However, background noise in combination with ethylbenzene

exposure showed OHC losses greater than the sum of the losses induced by noise and by ethylbenzene alone.

No reproductive or developmental studies in humans exposed to ethylbenzene by inhalation were located. However, a number of well conducted animal studies, cited in VCCEP (2007) and in AEGL (2008), tested for potential reproductive and developmental effects from airborne ethylbenzene exposure. In general, the studies suggested that developmental effects can occur at exposure concentrations greater than or equal to 1,000 ppm ethylbenzene. However, ethylbenzene is not a reproductive hazard. Considering that the primary acute odor-based ESL is quite low (i.e., 0.170 ppm in Table 2) and that the secondary acute health-based ESL (i.e., 6 ppm for ototoxicity in Table 2) is well below the developmental effects LOAEL of 1,000 ppm, the proposed acute ESLs are expected to also be protective of potential reproductive and developmental effects.

3.1.2 Mode of Action (MOA) and Dose Metric

Similar to other alkylbenzenes (i.e., toluene and xylene), ethylbenzene is readily absorbed by the lungs, distributed to tissues according to tissue blood flow and lipid content, metabolized by the liver, (primarily to mandelic acid and phenylglyoxylic acid) and rapidly excreted as urinary metablolites. The blood elimination kinetics of inhaled ethylbenzene show rapid elimination, evidenced by elimination half-times of 3.3 to 63 minutes. In addition, it has been reported that steady-state ethylbenzene/blood concentrations are reached within 2 h of initial exposure to ethylbenzene concentrations ranging between 75 and 500 ppm, as cited by Charest-Tardif et al. (2006).

Inhalation is the primary route of ethylbenzene exposure and ototoxicity is the critical endpoint.

Although the MOA underlying ethylbenzene's ototoxicity is not fully understood, Gagnaire et al. (2007) suggested that the observed ototoxicity is directly related to ethylbenzene rather than to a metabolite. Furthermore, specific dose metric data (e.g., blood concentration of parent chemical, area under blood concentration curve of parent compound, putative metabolite concentrations in blood or target tissue) are unavailable for the key study. Therefore, ethylbenzene exposure concentration will be used as the default dose metric. Ethylbenzene's ototoxicity is assumed to be a threshold effect (i.e., nonlinear MOA).

3.1.3 POD for the Key Study and Dosimetric Adjustment

Since the Cappaert et al. (2000) study results were presented graphically (e.g., no discernable standard deviations or standard errors), the NOAEL/LOAEL approach was chosen over the benchmark dose (BMD) model approach. In addition, the small number of animals per exposure group in the key study (8 per group) may not support statistical resolution of a benchmark response (i.e., the study should provide sufficient statistical power to detect a change of similar magnitude to the benchmark response) as suggested by Odin et al. (2005).

Ethylbenzene's pharmacokinetic half-life is very short, evidenced by its rapid detoxification (i.e., quickly absorbed and excreted). On the other hand, its pharmacodynamic half-life is quite long, evidenced by auditory system effects observed after a 3- to 6-week recovery period from only 5 days of ethylbenzene exposure. Since ethylbenzene's dynamic half-life is longer than its kinetic half-life, the pharmacodynamic factor appears to be the rate-determining step.

Since exposure concentration and duration play a role in producing ototoxicity, Haber's Rule as modified by ten Berge (1986) where n=3 was used to adjust the POD of 300 ppm for exposure duration.

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(300\ ppm)^3 \times (8\ h/1h)]^{1/3} = 600\ ppm = POD_{ADJ}$$

where: C_2 = desired concentration
C_1 = exposure concentration tested
T_1 = 8h exposure duration tested
T_2 = 1h desired exposure duration

Considering that ethylbenzene is relatively water soluble, and produces both local and systemic effects, it is classified as a Category 2 gas. However, since Category 2 gases are still under review by USEPA, the relevant dosimetry classification for ethylbenzene is a Category 3 gas since the critical effects were systemic. Therefore, the human equivalent concentration (POD_{HEC}) was obtained according to ESL guidelines (TCEQ 2006) 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

For ethylbenzene, the blood/gas partition coefficients for rats and humans are 42.7 and 28.0, respectively as reported by ATSDR (2007). Since ethylbenzene's blood/gas partition coefficient is greater for rats than for humans, the default value of 1 is used as the animal to human blood/gas ratio (USEPA 1994).

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / [(H_{b/g})_H] = 600\ ppm \times 1 = 600\ ppm$$

3.1.4 Adjustments of the POD_{HEC}

Since ethylbenzene's ototoxicity is assumed to be a threshold effect, uncertainty factors (UFs) were applied to the POD_{HEC}. An UF of 10 for intraspecies variability (UF_H) was used to account for sensitive subpopulations.

Since the interspecies variability factor has 2 components (i.e., pharmacokinetic and pharmacodynamic), and because the pharmacokinetic component was addressed in the POD_{HEC}

calculation, only the pharmacodynamic component remains as a partial interspecies uncertainty factor. Therefore, an UF of 3 for interspecies variability (UF_A) was chosen for uncertainty in extrapolating data from animals to humans.

A database UF of 1 (UF_D) accounts for ethylbenzene's extensive acute toxicological database. The total UFs applied were 30. The acute ReV was calculated as follows:

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 600 \text{ ppm} / (10 \times 3 \times 1)$$
$$= 20 \text{ ppm}$$
$$= 20{,}000 \text{ ppb}$$

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

The acute ReV value was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV is 86,000 µg/m^3 (20,000 ppb). At the target hazard quotient of 0.3, the ^{acute}ESL is 26,000 µg/m^3 (6,000 ppb) (Table 4).

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

Parameter	Summary
Study	Cappaert et al. (2000)
Study population	32 Wag/Rij rats
Study quality	High
Exposure Methods	8 h/5 days at inhalation exposures of 0, 300, 400, and 550 ppm
LOAEL	400 ppm
NOAEL	300 ppm
Critical Effect	Ototoxicity
POD_{HEC}	600 ppm (NOAEL)
Exposure Duration	8 h/5 days
Extrapolation to 1 h exposure	Concentration and duration dependent
Extrapolated 1 h concentration (POD_{ADJ})	600 ppm
Total Uncertainty Factors (UFs)	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	NA
Incomplete Database UF	1
Database Quality	High
Acute ReV [1 h] (HQ = 1)	**86,000 µg/m^3 (20,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**26,000 µg/m^3 (6,000 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Ethylbenzene is a colorless liquid with an aromatic-like odor. A 50% odor detection threshold value of 740 µg/m^3 (170 ppb) ethylbenzene was reported by Nagata (2003) utilizing the triangular odor bag method. Since ethylbenzene does not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

3.2.2 Vegetation Effects

No data were found to establish a vegetation-based ESL as a result of acute exposure to ethylbenzene in air.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

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

Acute ReV = 86,000 µg/m^3 (20,000 ppb)
^{acute}ESL = 26,000 µg/m^3 (6,000 ppb)

The acute ReV of 86,000 µg/m^3 (20,000 ppb) may be used for evaluation of air monitoring data (Table 1). The short-term ESL for air permit evaluations is the ^{acute}ESL of 26,000 µg/m^3 (6,000 ppb) (Table 2). The health-based ^{acute}ESL (HQ = 0.3) is not used for evaluation of air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Study

Physical/Chemical properties of ethylbenzene are discussed in Chapter 3.

Although chronic-duration inhalation exposures to ethylbenzene in humans are preferred, they are limited for reasons provided in Section 3.1.1. Due in part to limited human studies, an NTP (1999) 2-year inhalation study of ethylbenzene exposure in rats and mice was selected as the key study for chronic-duration exposure.

The NTP (1999) study exposed groups of 50 male and 50 female F344/N rats to 0, 75, 250, and 750 ppm ethylbenzene by inhalation for 6 h per day, 5 days per week, for 104 weeks. Animals were observed and clinical findings and body weights were recorded. A complete necropsy and microscopic examination of major tissues and organs were performed for all animals. Clinical findings were unaffected by ethylbenzene exposure. However, survival was significantly reduced only for males in the 750 ppm exposure group. Both sexes in the 750 ppm group had statistically significant high incidences of renal tubule adenoma and adenoma or carcinoma (combined). The neoplastic lesions will be discussed in the Carcinogenic Potential Section 4.2. Non-neoplastic lesions included a high incidence of renal tubule hyperplasia, which was statistically significant for both sexes in the 750 ppm group. However, the severity of the renal tubule hyperplasia was unaffected for either sex at all exposure groups.

Although the incidence of nephropathy was unaffected among both sexes at all exposure groups, increased severity of nephropathy was statistically significant for the 750 ppm exposure group males, and more importantly for females at all exposure groups. The severity of the nephropathy was graded moderate (grade = 3) to marked (grade = 4) for the 750 ppm group males (average grade = 3.5), and nephropathy was considered the likely contributor to the increased mortality for this exposure group. However, the severity of nephropathy was less for treated females and

ranged from minimal (grade = 1) to moderate (grade = 3). In addition, survival was unaffected for females at all exposure groups.

Both the incidence and severity of nephropathy were lower among females than among males. Furthermore, the severity of nephropathy was minimal (grade = 1) to mild (grade = 2) for the 75 ppm group females (average grade = 1.6). Also, the severity of nephropathy for the 75 ppm group females was similar to control group females (average grade = 1.3). Considering that the severity of nephropathy was minimal to mild, that clinical findings and survival were unaffected by treatment, and since the severity of nephropathy was similar to the control group, the 75 ppm exposure concentration was chosen as the NOAEL. Therefore, the NTP (1999) study identified the lowest NOAEL and the critical effect POD of 75 ppm based on increased severity of nephropathy.

The NTP (1999) study was chosen as the key study because it is a recently published well conducted study, it was chosen by ATSDR (2007) in its toxicological profile that developed a chronic MRL, and because it was chosen by Cal EPA (2000) for its chronic REL for non-neoplastic effects. In addition, U.S. EPA's IRIS (1991) ethylbenzene assessment for its chronic RfC was based on developmental toxicity studies using rats and rabbits (Andrew et al. 1981 and Hardin et al. 1981). The IRIS (1991) evaluation included a database uncertainty factor of 10 for a lack of a multigenerational reproductive study, and for a lack of chronic studies. However, both types of studies became available after the IRIS (1991) assessment.

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

Exposure concentration data for ethylbenzene is available from the NTP (1999) study. In addition, ethylbenzene's MOA for increased severity of nephropathy is not fully understood, and data on other more specific dose metrics are not available for the key study (e.g., blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue). Therefore, ethylbenzene exposure concentration will be used as the default dose metric.

4.1.3 POD for Key Study and Dosimetric Adjustment

Because the NTP (1999) study's nephropathy severity ratings were presented with no standard deviations or standard errors, the NOAEL/LOAEL approach was chosen over application of a benchmark dose (BMD) model approach. The NOAEL of 75 ppm for increased severity of nephropathy reported by NTP (1999) was chosen as the POD and was used to derive a chronic ReV. Considering the severity of nephropathy, that nephropathy was the likely contributor to increased mortality, and because there were essentially no histopathologic findings in a 13-week inhalation exposure study at doses between 100 ppm and 1,000 ppm (NTP 1992), both exposure concentration and duration are probable contributing factors.

Therefore, the POD was adjusted for continuous chronic exposure.

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

where: POD = POD from an animal study based on discontinuous exposure

D = exposure duration (h per day)

F = exposure frequency (days per week)

POD_{ADJ} = 75 ppm x (6/24 h) x (5/7 days) = 13.4 ppm

Since ethylbenzene is considered a Category 2 gas, and because Category 2 gases are still under review by USEPA, the relevant dosimetry classification for ethylbenzene is a Category 3 gas since the critical effects were systemic. Therefore, the human equivalent concentration (POD_{HEC}) was obtained according to ESL guidelines (TCEQ 2006) 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

Ethylbenzene's blood/gas partition coefficient is greater for rats than for humans, therefore the default value of 1 was used for the animal to human blood/gas ratio (USEPA 1994).

$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / [(H_{b/g})_H] = 13.4 \text{ ppm} \times 1 = 13.4 \text{ ppm}$

4.1.4 Selection of Critical Effect and Adjustment of POD_{HEC}

Severity of nephropathy was considered the critical effect. The MOA by which ethylbenzene produces increased severity of nephropathy has not been identified (Section 4.1.2). Therefore, the default approach for noncarcinogenic effects is to determine a POD and apply UFs to extrapolate from the POD to lower concentrations (i.e., assume a nonlinear MOA) in order to calculate a ReV.

To calculate the chronic ReV using the NTP (1999) study, the POD_{HEC} was divided by the appropriate uncertainty factors (UFs):

- An intraspecies UF (UF_H) of 10 to account for variation in sensitivity within members of the human population.
- Since the interspecies variability factor has 2 components (i.e., pharmacokinetic and pharmacodynamic), and the pharmacokinetic component has been addressed by the POD_{HEC} calculation, only the pharmacodynamic component remains. Therefore, a partial interspecies uncertainty factor of 3 for interspecies variability (UF_A) was chosen for extrapolating data from animals to humans.
- A database UF of 1 (UF_D) accounts for the extensive ethylbenzene toxicological database.

$ReV = POD_{HEC} / (UF_H \times UF_A \times UF_D) = 13.4 \text{ ppm} / (10 \times 3 \times 1) = 0.45 \text{ ppm}$

$ReV = 0.45 \text{ ppm} = 450 \text{ ppb } (1{,}900 \text{ µg/m}^3)$

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

The chronic ReV of 450 ppb (1,900 µg/m^3) was rounded to two significant figures at the end of all calculations. The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$ by using the following formula and a hazard quotient (HQ) of 0.3 (Table 5):

$^{chronic}ESL_{nonlinear(nc)} = \text{chronic ReV} \times HQ$

$^{chronic}ESL_{nonlinear(nc)} = 135 \text{ ppb } (570 \text{ µg/m}^3)$

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

Parameter	Summary
Study	2-year inhalation exposure in rats, NTP (1999)
Study Population	F344/N Rats – 50 per sex per group
Study Quality	High
Exposure Method	Inhalation – 0, 75, 250, and 750 ppm
Critical Effects	Increased severity of nephropathy
POD	75 ppm (NOAEL)
POD_{adj}	13 ppm
Exposure Duration	6 h/day, 5 days/week, for 104 weeks
POD_{HEC} Dosimetric adjustment to general population	13 ppm
Total UFs	30
Interspecies UF	3
Intraspecies UF	10
LOAEL to NOAEL UF	Not applicable
Subchronic to chronic UF	Not applicable
Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**1,900 µg/m^3 (450 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**570 µg/m^3 (135 ppb)**

4.2 Carcinogenic Potential

The following agencies evaluated ethylbenzene's carcinogenic potential: IARC (International Agency for Research on Cancer) - possibly carcinogenic to humans; USEPA (United States Environmental Protection Agency) - not classifiable as to human carcinogenicity; German MAK Commission - substances which cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data (i.e., database is insufficient for the establishment of an MAK value); ACGIH (American Conference of Governmental Industrial Hygienists) confirmed animal carcinogen with unknown relevance to humans (the above cited by ACGIH 2008).

IARC considered ethylbenzene as "possibly carcinogenic to humans" based on an NTP (1999) inhalation study in rats and mice (50 per sex) exposed to 0, 75, 250, and 750 ppm ethylbenzene for up to 2 years. The highest exposure concentration of 750 ppm produced increased mortality

in male rats, increased incidences of renal tubule neoplasms and testicular adenomas in male rats, increased incidences of renal tubule adenomas in female rats, increased incidences of alveolar/bronchiolar neoplasms in male mice, and increased incidences of hepatocellular neoplasms in female mice (ATSDR 2007). The NTP (1999) study concluded that there was clear evidence of carcinogenic activity in 750 ppm group male rats (e.g., increased renal tubule neoplasms), and a weaker evidence of carcinogenic activity in 750 ppm group female rats (e.g., increased renal tubule adenomas), in 750 ppm group male mice (e.g., increased alveolar/bronchiolar neoplasms), and in 750 ppm group female mice (e.g., increased hepatocellular neoplasms).

Hard (2002) re-evaluated the histopathology of rat kidneys from the NTP (1999) study and suggested that the increase in renal tumors observed in the 750 ppm group males may be related to chemically induced exacerbation of chronic progressive nephropathy, aided in part by a contributing factor in male rats associated with $\alpha_{2\mu}$-globulin nephropathy. Hard (2002) concluded that ethylbenzene induced exacerbation of chronic progressive nephropathy was the primary MOA underlying the development of renal neoplasia, a pathway that is considered to have no relevance for extrapolation to humans. Furthermore, a review of currently available genotoxicity data for ethylbenzene by Henderson et al. (2007) revealed that results from both *in vitro* and *in vivo* tests known to assess direct DNA damage have been predominantly negative in the absence of excessive toxicity. In addition, Henderson et al. (2007) concluded that available data do not support a genotoxic MOA for ethylbenzene induced kidney, liver, or lung tumors in rats and mice.

Furthermore, Gaylor (2005) reviewed 156 NTP chronic bioassays and found that 62% (97/156) of the chemicals tested were identified by the NTP as showing some or clear evidence of carcinogenicity. The lifetime exposure studies were typically conducted in rats and mice (50 per sex per group), incorporated the maximum tolerated dose (MTD), and included many non-genotoxic chemicals. Results of the investigation estimated the probability that almost all chemicals (e.g., 92%) would produce a statistically significant ($P \leq 0.01$) increase in tumor incidence with larger sample sizes (e.g., from 50 to 200 rats or mice per sex per group). The analysis suggested that exposure to the MTD can result in cytotoxicity, which can lead to increased carcinogenicity due to increased opportunities for mutagenic activity during the regenerative cell proliferation process. It also suggested that a chemical's carcinogenic activity may be related to one or more nearly universal MOAs (e.g., regenerative cell proliferation at the MTD) rather than to some unique carcinogenic property for the chemical. Considering that the NTP (1999) study was conducted with 50 per sex per group and that 750 ppm = MTD, the observed carcinogenic responses may be unrelated to inherent ethylbenzene carcinogenicity, but rather to some universal MOA operative at the MTD.

Evaluating carcinogenic potential using a WOE approach requires scientific judgment. Considering that the primary MOA underlying development of renal neoplasia is not relevant to humans as suggested by Hard (2002), that since the NTP (1999) study incorporated the MTD

may account for carcinogenic responses unrelated to ethylbenzene's inherent carcinogenic potential as suggested by Gaylor (2005), and because there is no reported association between occupational exposure to ethylbenzene and cancer in humans, the available data are insufficient to establish a carcinogenic endpoint with acceptable confidence. Furthermore, according to the ESL Guideline Hazard Assessment and WOE approach (TCEQ 2006, Section 4.5.1); a carcinogenic dose-response assessment is generally only performed if the chemical is considered "carcinogenic to humans" or "likely to be carcinogenic to humans". Therefore in the absence of clear carcinogenic evidence, ethylbenzene's carcinogenic response remains uncertain, and a carcinogenic-based ESL will not be derived at this time.

4.3 Welfare-Based Chronic ESL

No data were found to establish a vegetation-based ESL as a result of chronic exposure to ethylbenzene in air.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The long-term evaluation for ethylbenzene resulted in the derivation of the following chronic values:

chronic ReV = 1,900 µg/m^3 (450 ppb)
$^{chronic}ESL_{nonlinear(nc)}$ = 570 µg/m^3 (135 ppb)

The chronic ReV of 1,900 µg/m^3 (450 ppb) is used for evaluation of long-term ambient air monitoring data (Table 1). The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ of 570 µg/m^3 (135 ppb) (Table 2). The health-based $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used for evaluation of air monitoring data.

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Chapter 5 References

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