Development Support Document
Final, September 30, 2016

Heptane, All Isomers

CAS Registry Number:
n-Heptane: 142-82-5
Other 8 Isomers

Prepared by

Jong-Song Lee, Ph.D.

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AMCV	air monitoring comparison value
^{o}C	degrees Celsius
CNS	central nervous system
DSD	development support document
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
$^{chronice}ESL_{generic}$	chronic health-based effects screening level for chemicals not meeting minimum database requirements
$^{chronic}ESL_{threshold(c)}$	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
FOB	functional observational battery
GD	gestation day
GLP	good laboratory practice
h	hour(s)
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human

Acronyms and Abbreviations	Definition
mm Hg	millimeters of mercury
HEC	human equivalent concentration
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
LEL	lower explosive limit
LOAEL	lowest-observed-adverse-effect-level
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(s)
MOA	mode of action
NOAEL	no-observed-adverse-effect-level
OECD	Organization for Economic Cooperation and Development
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% depression in respiratory rate
ReV	reference value
RGDR	regional gas dose ratio
SD	Sprague-Dawley rats
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division

Acronyms and Abbreviations	Definition
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

Chapter 1 Summary Tables and Figure

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 n-heptane. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015a) for an explanation of 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 physical/chemical data for n-heptane.

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

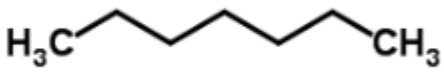
Short-Term Values	Concentration	Notes
Acute ReV [1-h]	34,000 µg/m^3 (8,200 ppb) **for n-heptane and isomers**	**Critical Effect:** Transient behavioral impairments in mice
$^{acute}ESL_{odor}$	---	Gasoline-like odor, not pungent or disagreeable
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	9,000 µg/m^3 (2,200 ppb) **for n-heptane and isomers**	**Critical Effect:** Free-standing NOAEL due to lack of decrease in body weight gain, neuromuscular function, and neurotoxic effects observed in rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3)	10,000 µg/m^3 (2,500 ppb)[a] **for n-heptane and isomers Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Transient behavioral impairments in mice
^{acute}ESL$_{odor}$	---	Gasoline-like odor, not pungent or disagreeable
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	2,700 µg/m^3 (660 ppb)[b] **for n-heptane and isomers Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Free-standing NOAEL due to lack of decrease in body weight gain, neuromuscular function, and neurotoxic effects observed in rats
^{chronic}ESL$_{nonthreshold(c)}$ ^{chronic}ESL$_{threshold(c)}$	---	Inadequate information to assess carcinogenic potential
^{chronic}ESL$_{veg}$	---	No data found

[a] Based on the acute ReV of 8,200 ppb multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.
[b] Based on the chronic ReV of 2,200 ppb multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

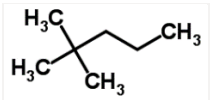
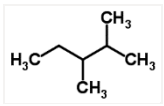
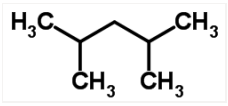
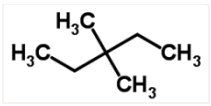
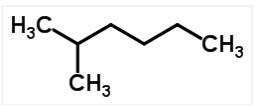
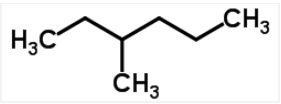
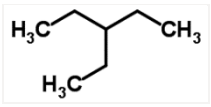
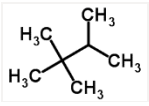
Table 3 Chemical and Physical Data

Parameter	n-Heptane	Reference
Chemical Structure		ChemSpider
Molecular Weight	100.2	ACGIH (2001)
Molecular Formula	C_7H_{16}	ACGIH (2001)
Structural Formula	CH_3-$(CH_2)_5$- CH_3	ACGIH (2001)
Physical State	Liquid	ACGIH (2001)
Color	Colorless	ACGIH (2001)
Odor	Gasoline-like odor	ACGIH (2001)
CAS Registry Number	142-82-5	ACGIH (2001)
Synonyms/Trade Names	Heptane; dipropylmethane; heptyl hydride	ACGIH (2001)
Solubility in water @25°C	Practically insoluble (3.40 mg/L)	ACGIH (2001)
Log K_{ow}	4.66	IPCS 1997
Vapor Pressure @25°C	47.7 mm Hg	ACGIH (2001)
Vapor density (air = 1)	3.45	IPCS (1997)
Density/Specific Gravity (water = 1)	0.673 to 0.698 @ 20°C	ACGIH (2001)
Melting Point	-98.4°C	ACGIH (2001)
Boiling Point	125.7°C	ACGIH (2001)
Lower Explosive Limit (LEL)	1.1-6.7 %	IPCS (1997)
Conversion Factors	1 ppm = 4.1 mg/m^3 1 mg/m^3 = 0.24 ppm	TCEQ

Chapter 2 Major Sources and Uses

Heptane is a colorless, volatile, flammable organic liquid with a faint hydrocarbon odor and is only slightly soluble in water. There are 9 isomers of heptane including n-heptane, 2,2-, 2,3-, and 2,4-dimethylpentane, 2,2,3-trimethylbutane, and 2- and 3-methylhexane (Table 4).

Table 4 Isomers of Heptane and CAS No.

Isomer Name	CAS No.	Chemical Structure
n-heptane	142-82-5	
2,2-dimethylpentane	590-35-2	
2,3-dimethylpentane	565-59-3	
2,4-dimethylpentane	108-08-7	
3,3-dimethylpentane	562-49-2	
2-methylhexane	591-76-4	
3-methylhexane	589-34-4	
3-ethylpentane	617-78-7	
2,2,3-trimethylbutane	464-06-2	

Heptane is a component of natural gas and crude oil (0.1-1.9%). All isomers of heptane are used as solvents for glues, lacquers and inks, as industrial solvent for extracting natural gas, in organic synthesis, as an anesthetic, and are ingredients of gasoline and petroleum solvents. n-Heptane is a standard for octane rating measurement and 2,2,3-trimethylbutane is used in aviation fuel. Heptane is also produced commercially by fractional distillation of hydrocarbon feedstock.

Heptane can be released into the air from its production and use in many products associated with the petroleum and natural gas industries. In addition, the combustion of gasoline is a major mechanism for the release of heptanes into the atmosphere. Typical heptane daily ambient

concentrations for urban areas in the United States are between 0-140 parts per billion (ppb) (USEPA 1989).

In Texas, the highest reported 1-hour (h) concentration (from 2013 through 2014) of n-heptane was 23.28 ppb collected from AutoGC samples at an ambient air monitoring site at Decatur, Texas. The corresponding annual average concentrations were 0.05 and 0.03 ppb, respectively, in 2013 and 2014. The highest reported 24-h concentration of n-heptane in the state of 23.28 ppb (from 2013 to 2014) was measured at the Denton Airport, Texas monitor that collects 24-h canister samples every sixth day (d). The annual average concentrations measured at the Denton Airport monitor in 2013 and 2014 were 0.59 and 0.84 ppb, respectively.

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

n-Heptane is the most common isomer of heptane. The main chemical and physical properties of n-heptane are summarized in Table 3. Chemical and physical properties for other heptane isomers are similar to n-heptane.

3.2 Health-Based Acute 1-Hour ReV and ESL

No human studies are available concerning the acute adverse effects of heptane. n-Heptane has a low acute toxicity in experimental animals. Acute effects are considered similar to those of other saturated aliphatic hydrocarbons of similar carbon chain length (C_3-C_8) (HSDB 2013). Short-term inhalation of sufficiently high concentrations of n-heptane causes irritation of respiratory tract, neurobehavioral effects, loss of auditory sensitivity, narcosis, and respiratory arrest in mice and rats (Glowa 1991, Swann et al. 1974, Simonsen and Lund 1995). The narcotic effect of n-heptane in mice was observed at 10,000-15,000 ppm within 30-50 minutes (min) (Fuhner 1921, as cited in ACGIH 2001). TCEQ chose the well-conducted Glowa (1991) study as the key study. Other animal studies were used as supporting studies.

3.2.1 Key Animal Study (Glowa 1991)

Glowa (1991) examined the ability of n-alkanes (C_5-C_8), including n-heptane, to impair performance (neurobehavioral effects) and to stimulate the hypothalamic-pituitary-adrenal (HPA) axis (neuroendocrine effects) in adult male CD-1 mice (35-40 grams (g)).

For the behavioral effects assessment, impaired performance was assessed by studying operant response maintained under a fixed interval (FI) 60-second schedule of milk presentation. In the presence of flashing green lights, the first response to occur after the elapse of a 60-second interval produced milk. Eight mice were studied. Individual concentration-effect functions were obtained by comparing pre-exposure (control) levels of response to response after 30-minutes (min) of exposure of incrementally increased n-heptane concentrations. Recovery was determined 30 min following removal from exposure. Concentration was increased from 100 ppm (nominal concentrations) until response was abolished. The results showed that

concentrations of 1,000-3,000 ppm n-heptane occasionally increased rates of response. The rate of response was decreased 50% at 4,500 ppm, and was virtually abolished (100%) at 5,600 ppm. Following exposures of 10,000 ppm, mice were observed to be engaged in circular locomotive activity. Response recovered to 75% of control levels 30 min following ceasing exposure to 10,000 ppm n-heptane. The concentration-effect function was steep. Mean concentrations (± std dev) to result in a 50% and 10% rate of response-decreasing potency (EC_{50} and EC_{10}) were 3,872 ± 917 and 2,945 ± 1,199 ppm, respectively. Concentrations of 1,000-3,000 ppm n-heptane occasionally increased rates of response indicating the NOAEL could be > 1,000 and up to 3,000 ppm. The level of 2,945 ppm (EC_{10}) was considered a minimal LOAEL for transient behavioral impairment. The TCEQ considers the EC_{10} of 2,945 ppm an analogue to a benchmark concentration at 10% response (BMC_{10}).

For the neuroendocrine effects assessment, the effect on HPA axis activation was studied following inhalation exposure of mice (4-6 mice per concentration) to n-heptane (100 to 10,000 ppm) for 30 min. Immediately after exposure ceased, animals were sacrificed and the adrenocortocotropin (ACTH) levels in serum were measured. ACTH levels were similarly increased from 100 to 3000 ppm, approximately 200-400% of the control. The ACTH level increased to approximately 750% of the control at 10,000 ppm. However, no statistical analyses were performed and thus, statistical significance is unknown. Without knowing the biological significance of the neuroendocrine effects as measured by HPA activation, or the statistical significance of the effects, we could not determine if the effects were adverse.

The minimal LOAEL/ BMC_{10} of 2,945 ppm for transient behavioral impairment was used as point of departure (POD) to develop the acute ReV for n-heptane.

3.2.2 Supporting Animal Studies

3.2.2.1 Swann et al. (1974)

Swann et al. (1974) studied the respiratory tract irritation properties of n-heptane in male Swiss mice (25 g). Four animals were exposed head-only for 5 min at each of the following concentrations of heptane: 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, and 48,000 ppm (nominal concentrations). The respiratory rate, depth, and configuration were counted and recorded for 15-second intervals while the animals were inhaling n-heptane. Concentrations up to 16,000 ppm produced no irritation. At 16,000 ppm, mice experienced irritation and considerable body movement during exposure. At 32,000 ppm, mice experienced respiratory irregularity during exposure with deeper anesthesia during recovery. At 48,000 ppm, mice experienced considerable sensory and motor irritation and irregular respiration, three-fourths of the mice stopped breathing within 3.75 min of the onset of exposure. A NOAEL and LOAEL of 8,000 and 16,000 ppm, respectively, for irritation were identified from this study. Since the exposure duration was only 5 min, the NOAEL was not used as a POD to develop the acute ReV and ^{acute}ESL.

3.2.2.2 Simonsen and Lund (1995)

In a 4-week subacute inhalation study for ototoxicity by Simonsen and Lund (1995), male Long Evans rats were exposed to n-heptane at 0 (9 rats), 800 (11 rats), and 4,000 (10 rats) ppm (target concentrations) for 6 h/d for 28 consecutive days. The mean analytical concentrations were 0, 801 ± 79 and 4,006 ± 242 ppm. The function of the auditory system was examined by measurements of auditory brain stem response (ABR). The results showed that the mean body weight gain in exposed rats, from the cessation of exposure over the remaining 8 weeks experiment, was lower than controls, The difference in body weight gain between the control and 4,000 ppm group was statistically significant. Exposure to 4,000 ppm n-heptane statistically significantly reduced the amplitudes of components Ia and IV of the ABR. The reduction in ABR corresponds to an increase in the auditory threshold of approximately 10 dB at all frequencies. No significant changes in ABR were observed in the group exposed to 800 ppm. A NOAEL of 800 ppm and a LOAEL of 4,000 ppm for decreased body weight gain and loss of auditory sensitivity were identified from this study. The 28-d NOAEL of 800 ppm was not used as a POD to derive acute toxicity values because adequate acute (<24 hours) data were available (TCEQ 2015a).

3.2.3 Reproductive and Developmental Toxicity Studies

No information on the potential of heptane to cause reproductive/developmental toxicity from oral or inhalation studies in humans or animals is available. In a dominant-lethal inhalation study with Isopar C (85% isooctane) performed by Bio/dynamics Inc. on behalf of Exxon Corporation in 1978 and submitted to USEPA in 1987 (Exxon 1987), the embryotoxic and/or teratogenic potential was evaluated using groups of 20 mated Sprague Dawley (SD) rats. Two groups were exposed to 400 and 1,200 ppm Isopar C on days 6 to 15 of gestation (GD 6-15). Female rats were sacrificed on GD 21, and fetuses were evaluated for external, soft tissue, and skeletal malformations. The study concluded that Isopar C was neither embryotoxic nor teratogenic at inhalation concentrations up to 1,200 ppm. Similarly, Isopar C did not induce reproductive effects (implantation/pregnancy rate changes) in female rats or affect reproductive organ development in male rats at the same inhalation exposure concentration. OECD (2010) conducted a weight-of-evidence analysis using available data from the inhalation reproductive/developmental toxicity studies from isooctane and other analogous substances. The data analysis showed no evidence that exposure to compounds in the C_7-C_9 aliphatic hydrocarbon category resulted in reproductive/developmental toxicity. Accordingly, the TCEQ does not expect reproductive/developmental toxicity occurs from exposure to heptane.

3.2.4 Mode of Action (MOA) Analysis and Dose Metric

n-Heptane is readily absorbed and distributed throughout the body. Pharmacokinetic studies in rats (Bahima et al. 1984 and Perbellini et al. 1986) showed that n-heptane is metabolized to hydroxy derivatives via a cytochrome p450 oxidase system. 2-Heptanol and 3-heptanol were the major metabolites (> 80%) and were rapidly excreted as sulfates and glucuronides in the urine. 2,5-Heptanedione, which is neurotoxic, was the metabolite found in a relatively small amount (approximate 0.1 and 0.8% of total urinary metabolites, respectively, in the Bahima et al. 1984

and Perbellini et al. 1986 studies). Thus, n-heptane is expected to be relatively low in neurotoxicity. The MOA analysis was not applicable due to lack of general non-carcinogenic neurotoxic effects observed in animal studies. Data on the exposure concentration of the parent chemical are available, whereas data on more specific dose metrics are not available. Thus, exposure concentration of the parent chemical will be used as the dose metric.

3.2.5 POD and Critical Effect

For n-heptane, the acute NOAEL/BMC_{10} of 2,945 ppm based on a 30-min inhalation mouse study (Glowa 1991) was used as the POD to develop the acute ReV. The critical effect was transient behavioral impairment.

3.2.6 Dosimetric Adjustments

3.2.6.1 Exposure Duration Adjustments

The POD from the key study (2,945 ppm) was adjusted from a 30-min exposure duration to 60-min (1-h) exposure duration using Haber's rule as modified by ten Berge (1986) (TCEQ 2015a).

$$POD_{ADJ} = C_2 = (C_1) \times (T_1 / T_2)$$
$$= (2{,}945 \text{ ppm}) \times (30 \text{ min} / 60 \text{ min})$$
$$= 1{,}472.5 \text{ ppm}$$

3.2.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

n-Heptane is practically water insoluble. Acute exposures to n-heptane cause transient behavioral impairment and neurological function impairment, respectively, which are systemic effects. In addition, toxicokinetic data on n-heptane indicate that n-heptane is rapidly absorbed via the lungs and widely distributed within the body. n-Heptane was therefore considered a Category 3 gas (USEPA 1994). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

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

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

The measured blood/air partition coefficient in human ($(H_{b/g})_H$) and in the rat ($(H_{b/g})_A$) for n-heptane are 2.38 and 4.75, which were reported by Meulenberg and Vijverberg (2000). Because the ratio of the animal-to-human partition coefficients (4.75/2.38 = 1.99) is greater than one, a default value of one is used as the regional gas dose ratio (RGDR) (i.e., $((H_{b/g})_A / ((H_{b/g})_H)$ as recommended by TCEQ (2015a). The resulting POD_{HEC} from the POD_{ADJ} of 1,472.5 ppm in the Glowa (1991) rat study is 1472.5 ppm for n-heptane.

3.2.7 Adjustments of the POD_{HEC}

The POD_{HEC} of 1472.5 ppm was used to derive the acute ReV and ^{acute}ESL for n-heptane. The following UFs were applied to the POD_{HEC} (total UF = 180):

- a UF_H of 10 for intraspecies variability,
- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences,
- a UF_L of 2 was used to adjust the LOAEL to NOAEL because the LOAEL was based on a mild effect (i.e., transient behavioral impairment), and
- a UF_D of 3 was used for uncertainty associated with an incomplete database because human studies for pure n-heptane were not available, the endpoints evaluated in animals predominately concerned neurotoxicity, and the only study evaluating reproductive/developmental effects was for another C_7-C_9 aliphatic hydrocarbon (e.g., isooctane). However, a value of 6 was not used because animal studies were conducted examining different toxicity endpoints, two inhalation bioassays in two animal species were available, confidence in the database is considered medium-high. The quality of the key rat study is high.

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$
$$= 1472.5 \text{ ppm} / (10 \times 3 \times 2 \times 3)$$
$$= 8.180 \text{ ppm}$$
$$= 8{,}200 \text{ ppb (rounded to two significant figures)}$$

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

In deriving the acute ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV was then used to calculate the ESL, and the ESL subsequently rounded. The ^{acute}ESL of 2,500 ppb (10,000 µg/m^3) for n-heptane is based on the acute ReV of 8,200 ppb (34,000 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations. Table 5 summarizes the derivation of acute toxicity factors for n-heptane.

Table 5 Summary of Acute ReV and ^{acute}ESL for n-Heptane

Parameter	Values and Descriptions
Study	Glowa (1991)
Study Quality	High
Study Population	adult male CD-1 mice (4-6 mice/group)
Exposure Method	Incrementally increasing exposure inhalation from 100 ppm up to 10,000 ppm (nominal concentrations)
Exposure Duration	30 min
Critical Effects	Transient behavioral impairment ≥ 2,945 ppm
POD	2,945 ppm (a minimal LOAEL/BMC_{10})
POD_{ADJ} to 1h	1472.5 ppm
POD_{HEC}	1472.5 ppm
Total UFs	180
Intraspecies UF	10
Interspecies UF	3
LOAEL to NOAEL UF	2
Incomplete Database UF	3
Database Confidence	Medium to high
Acute ReV [1 h] (HQ = 1)	**8,200 ppb (34,000 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**2,500 ppb (10,000 µg/m^3)**

3.3 Health-Based Acute 24-Hour ReV

Consistent with TCEQ Guidelines (TCEQ 2015a), the potential need for a 24-h ReV was evaluated. However, monitored 24-h concentrations of n-heptane and isomers across Texas (TAMIS 2005-2015) were ≥ 63 times below the chronic ReV of 2,200 ppb. Therefore, a 24-h ReV is not needed and is not derived in this DSD.

3.4 Welfare-Based Acute ESLs

3.4.1 Odor Perception

n-Heptane has a gasoline-like odor. Odor detection thresholds of 150 and 220 ppm for n-heptane have been reportedby Amoore and Hautala (1983) and May (1966) , respectively. Nagata (2003)

reported an odor detection threshold of 0.67 ppm for n-heptane. Since heptane and isomers do not have pungent or disagreeable odors, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015b).

3.4.2 Vegetation Effects

No information was found to indicate that special consideration should be given to possible vegetation effects from n-heptane and isomers.

3.5 Short-Term ESLs and Values for Air Monitoring Data Evaluations

3.5.1 n-Heptane

The acute evaluation resulted in the derivation of the following values for n-heptane:

- Acute ReV = 34,000 µg/m^3 (8,200 ppb)
- ^{acute}ESL = 10,000 µg/m^3 (2,500 ppb)

For the evaluation of ambient air monitoring data, the acute ReV of 34,000 µg/m^3 (8,200 ppb) is used (Table 1). The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 10,000 µg/m^3 (2,500 ppb) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5.2 Other Heptane Isomers

No acute toxicity data were available describing the potential acute toxicity of other heptane isomers. For the purpose of effects evaluations for air permit applications and/or ambient air monitoring data, the acute ReV and ESL of 34,000 and 8,200 µg/m^3 for n-heptane were used as a surrogate. The generic acute ReV and ESL for other isomers are based on their structure-activity similarity to that for n-heptane.

3.6 Acute Inhalation Observed Adverse Effect Levels (IOAELs)

The acute inhalation observed adverse effect level (^{acute}IOAEL) for n-heptane was based on the minimal $LOAEL_{HEC}$ of 2,945 ppm (LOAEL of 2,945 ppm x RGDR of 1) determined from the mouse study (Glowa 1991). No duration adjustment was made although an animal-to-human dosimetric adjustment was performed. Effects occurred in some animals and represent a concentration at which 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 ^{acute}IOAEL level is provided for informational purposes only (TCEQ 2015a). The ^{acute}IOAEL for n-heptane and isomers is:

- ^{acute}IOAEL = 11,900 mg/m^3 (2,900 ppm) (rounded to 2 significant figures)

The margin of exposure between the ^{acute}IOAEL (2,900 ppm) and the acute ReV (8.1 ppm) for n-heptane is approximately a factor of 358.

Chapter 4 Chronic Evaluation

4.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1 and Table 3.

4.2 Health-Based Toxicity Factors

OECD (2010) reported that repeated dose inhalation studies conducted on C_7-C_9 aliphatic hydrocarbons showed a low order of systemic toxicity. No overt clinical signs of neurotoxicity were observed in repeated dose inhalation studies in animals with n-heptane (Takeuchi et al. 1981) or n-nonane (Carpenter et al. 1978), or in repeated dose oral studies with n-octane or n-nonane (OECD 2010). Neurotoxicity of alkanes is correlated with the rate of metabolism to potentially neurotoxic gamma-diketones. The only generally significant adverse effect observed was transient CNS depression in some studies. CNS effects generally occurred within the first few days of exposure and abated by the second week of study, and these effects did not appear to worsen with longer exposures (API 1980, Carpenter et al. 1978). Several subchronic and chronic inhalation toxicity studies were reported for n-heptane (Frontali et al. 1981; Takeuchi et al. 1980; Bahima et al. 1984; Bio/Dynamics 1980).

4.2.1 Key Animal Study- Frontali et al. (1981)

Frontali et al. (1981) conducted a chronic inhalation neurotoxicity study in groups of 6-9 SD rats (230-260 g), exposed to 0 (control) and 1,500 ppm n-heptane for 9 h/d, 5 d/week for 30 weeks. At weekly or monthly intervals the rats were weighed and subjected to a physiological test of neuromuscular function as measured by the hindlimb spread on the landing. No statistically significant decrease in body weight gain was noted in both the two-way analysis of variance ($p = 0.47$) and the Student's *t*-test ($p = 0.14$). No statistically significant differences between the mean values for the hindlimb spreads observed in control and treated rats. No morphological giant axonal degradation was observed by histological examination of the nerve tissue. None of the animals developed signs of neuropathy. A free-standing NOAEL of 1,500 ppm n-heptane for decrease in body weight gain, neuromuscular function and neurotoxic effects (peripheral neuropathy) was identified from this study. The free-standing NOAEL was used as the POD to develop the chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

4.2.2 Supporting Studies

4.2.2.1 Takeuchi et al. (1980)

In a chronic comparative study of the neurotoxicity of n-heptane, groups of seven male Wistar rats (308 ± 18 g) were exposed by inhalation to 0 (control) and 3,000 ppm n-heptane for 12 h/d, 7 d/week for 16 weeks. The measured concentrations were 2,960 ± 200 ppm (mean ± std dev). The conduction velocity of tail nerves was measured before the exposure and after exposure for 4, 8, 12, and 16 weeks to determine the functional status of the peripheral nerves. There was a statistically significant decrease in body weight gain between the exposure group and the

controls after 8 weeks exposure. The body weight gain, however, gradually increased after 8 weeks and there were no statistically significant differences after 12 and 16 weeks exposure. No abnormal changes in behavior in exposure group or the controls. No particular changes in the nerve fibers and the peripheral nerve or alteration of motor conduction velocity were observed in rats exposed to n-heptane. Thus, a free-standing subchronic LOAEL of 2,960 ppm n-heptane for decrease in body weight gain was identified from this study. The LOAEL supports the NOAEL of 1,500 ppm identified from the Frontali et al. (1981) key study.

4.2.2.2 Bahima et al. (1984)

Bahima et al. (1984) exposed female Wistar rats (6/group) to 0 or 2,000 ppm 99% pure n-heptane by inhalation for 6 h/d, 5 d/week for 12 weeks. Results of this study showed that n-heptane was metabolized mainly by hydroxylation at ω-1 carbon atom and to a lesser extent at the ω-2 carbon atom. 2-Heptanol, 6-hydroxy-2-heptanone and 3-heptanol were the major metabolites (>70%) and were excreted as sulfates and glucuronides. 2,5-Heptanedione, which is neurotoxic, was the metabolite found in the least amounts (0.1%) in the urine. No clinical evidence of peripheral neuropathy (ataxia, loss of equilibrium, or weakened hind- and forelimbs) was observed in rats after 4, 8, and 12 weeks of exposure to n-heptane. The lack of neurotoxicity appears to be correlated to low production of 2,5-heptanedione. A free-standing NOAEL of 2,000 ppm for neurotoxicity was identified from this study. The NOAEL is higher than identified from the Frontali et al. (1981) key study for the same health endpoints.

4.2.2.3 Bio/Dynamic (1980)

In an unpublished inhalation study by Bio/Dynamics (1980, as cited in USEPA 1989), Male and female SD rats (15/sex/group) were exposed to 0, 400 or 3,000 ppm (target concentrations) 98.5% n-heptane 6 h/d, 5 d/week for 26 weeks. There was a 2-week post exposure recovery period. No treatment-related effects were observed in weekly observation for body weight, hematology or urinalysis. No evidence of neurological disturbances or organ toxicity was found. Five males and 5 females were examined for clinical chemistry at week 26. Except for increased serum alkaline phosphatase levels in female rats at 3,000 ppm ($p<0.05$), blood chemistry showed no hematological, renal, or liver abnormalities. In the absence of other adverse effects, increased serum alkaline phosphatase levels are not considered to be adverse effects; therefore, 3,000 ppm was considered a NOAEL for systemic effects.

4.2.3 MOA Analysis and Dose Metric

The MOA analysis was not applicable due to lack of general non-carcinogenic neurotoxic effects observed in a subchronic/chronic animal studies. There appears to be a very low rate of metabolism to gamma-diketones for n-alkanes and no such metabolism for isoalkanes (OECD 2010). Therefore, as a default for non-carcinogenic effects, a threshold, nonlinear assessment is conducted (TCEQ 2015a). Data on the exposure concentration of the parent chemical are available, whereas data on more specific dose metrics are not available. Thus, exposure concentration of the parent chemical will be used as the default dose metric.

4.2.4 POD and Critical Effect

The free-standing NOAEL of 1,500 ppm n-heptane for no decrease in body weight gain and absence of neurotoxic effects based on a 30-week inhalation rat study (Frontali et al. 1981) was used as the POD to develop the chronic ReV. The critical effects were no decrease in body weight gain and the absence of neuromuscular function and neurotoxic effects (peripheral neuropathy).

4.2.5 Dosimetric Adjustments

4.2.5.1 Exposure Duration Adjustments

The POD of 1,500 ppm was adjusted from a discontinuous exposure (9 h/d for 5 d/week) to continuous exposure concentration.

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

where:

D = Exposure duration, h per day

F = Exposure frequency, days per week:

POD_{ADJ} = 1,500 ppm x (9/24) x (5/7) = 401.785 ppm

4.2.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

n-Heptane is practically water insoluble. The endpoints studied by Frontali et al. (1981) were for systemic rather than POE effects. n-Heptane was considered a Category 3 gas. As described in Section 3.2.2.5.2, because the ratio of $((H_{b/g})_A$ /$((H_{b/g})_H)$ (4.75/2.38 = 1.99) is greater than one, a default value of one is used as the RGDR. The resulting POD_{HEC} from the POD_{ADJ} of 401.785 ppm in the Frontali et al. (1981) rat study is 401.785 ppm for n-heptane.

4.2.6 Adjustments of the POD_{HEC}

The POD_{HEC} of 401.785 ppm was used to derive the chronic ReV and ^{chronic}ESL for n-heptane. The following UFs were applied to the POD_{HEC} (Total UF = 180):

- a UF_H of 10 for intraspecies variability,
- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences,
- a UF_D of 6 was used for uncertainty associated with an incomplete database because 4 animal studies were conducted for different toxicity endpoints although only one animal species was used. No human studies for pure n-heptane were available and the critical effects were no decrease in body weight gain and absence of neurotoxicity. However, a value of 10 was not used because the endpoints evaluated in animals predominately concerned neurotoxicity, and studies evaluating reproductive/developmental toxicity were conducted in C_7-C_9 n-alkanes,

e.g., for octane, isooctane, and n-nonane, with toxicity similar to n-heptane (OECD 2010). However, a value of 10 was not used because the endpoints evaluated in animals predominately concerned neurotoxicity, and studies evaluating reproductive/developmental toxicity were conducted in C7-C8 n-alkanes. A study evaluating reproductive/developmental effects was available in one species for other C_7-C_9 aliphatic hydrocarbon (e.g., isooctane). Consistent with TCEQ (2015a), confidence in the database is considered medium to high. The quality of the key rat study is medium to high.

Chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 401.785 ppm / (10 x 3 x 6)
= 2.2321 ppm
= 2,200 ppb (rounded to two significant figures)

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

The $^{chronic}ESL_{threshold(nc)}$ of 660 ppb (2,700 µg/m^3) for n-heptane is based on the acute ReV of 2,200 ppb (9,000 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations. Table 6 summarizes the derivation of chronic toxicity factors for n-heptane.

Table 6 Summary of Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for n-Heptane

Parameter	Values and Descriptions
Study	Frontali et al. (1981)
Study Quality	Medium to high
Study Population	6-9 SD rats (230-260 g)
Exposure Method	0 (control) and 1,500 ppm (target concentrations)
Exposure Duration	9 h/d, 5 d/week for 30 weeks
Critical Effects	Absence of effects on body weight gain, neuromuscular function, and neurotoxicity
POD	1,500 ppm (free-standing NOAEL)
POD_{ADJ}	401.785 ppm
POD_{HEC}	401.785 ppm
Total UFs	180
Intraspecies UF	10
Interspecies UF	3
Incomplete Database UF	6
Database Quality	Medium to high
Chronic ReV [1 h] (HQ = 1)	**2,200 ppb (9,000 µg/m^3)**
$^{chronic}ESL$ [1 h] (HQ = 0.3)	**660 ppb (2,700 µg/m^3)**

4.3 Carcinogenic Potential

No data were found on long-term the carcinogenicity of heptane. n-Heptane has not been shown to be genotoxic or mutagenic. Brooks et al. (1988, as cited in USEPA IRIS) reported that n-heptane gave negative results in several genotoxicity assays. The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of heptane. The American Conference of Governmental Industrial Hygienists (ACGIH) has not assigned a carcinogenicity designation to this chemical. According to the Guidelines for Carcinogen Risk Assessment (USEPA 2005), the database for heptane provides "inadequate information to assess carcinogenic potential" because no epidemiological studies in humans and no chronic bioassay studies are available that assess the carcinogenic effects of heptane. Thus, a $^{chronic}ESL_{nonthreshold(c)}$ was not developed.

4.4 Welfare-Based Chronic ESL

No information was found to indicate that special consideration should be given to possible chronic vegetation effects from heptane.

4.5 Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

4.5.1 n-Heptane

The chronic evaluation resulted in the derivation of the following values for n-heptane:

- Chronic ReV = 9,000 µg/m^3 (2,200 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 2,700 µg/m^3 (660 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 9,000 µg/m^3 (2,200 ppb) is used (Table 1). The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{threshold(nc)}$ of 2,700 µg/m^3 (660 ppb) (Table 2). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5.2 Other Heptane Isomers

No chronic toxicity data were available describing the potential chronic toxicity of 6 other heptane isomers. For the purpose of effects evaluations for air permit applications and/or ambient air monitoring data, the chronic ReV and ESL of 9,000 and 2,700 µg/m^3 for n-heptane were used as a surrogate.

4.6 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)

No chronic LOAEL was reported and thus, the $^{chronic}IOAEL$ for n-heptane was not derived.

Chapter 5 References Cited in DSD

American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Documentation of the Threshold Limit Values for Octane, All Isomers. Cincinnati, OH.

American Petroleum Institute (API) (1980). A 26 Week Inhalation Toxicity Study of Heptane in the Rat. American Petroleum Institute Study No. 78-7233.

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

Bahima J, Cert A and Menéndez-Gallego M (1984). Identification of volatile metabolites of inhaled n-heptane in rat urine. Toxicol Appl Pharmacol 76, 473-482.

Boyes WK, WM Oshiro, H El-Masri et al. 2010. Acute inhalation of 2,2,4-trimethylpentane alters visual evoked potentials and signal detection behavior in rats. Neurotoxicol Teratol 32(5):525-35.

ChemSpider. 2016. Search and share chemistry. Available from: http://www.chemspider.com/Chemical-Structure.8560.html

Frontali N, MC Amantini MC, A Spagnolo et al. 1981. Experimental neurotoxicity and urinary metabolites of the C5-C7 aliphatic hydrocarbons used as glue solvents in shoe manufacture. Clin Toxicol 18(12):1357-1367.

Exxon Company. 1987. Eight toxicity reports on 2,2,4-trimethyl pentane (isooctane) with attachments and cover letter dated 072987. NTIS Report No. OTS0515208. 1-660.

Glowa, J. 1991. Behavioral toxicology of volatile organic solvents. V. Comparisons of the behavioral and neuroendocrine effects among n-alkanes. J Am Coll Toxicol 10(6): 639-646.

Hazardous Substance Databank (HSDB). 2016. Health and environmental database available via ToxNet of the National Library of Medicine, Bethsda, MD. Available from: (n-Octane) and (Isooctane)

International Programme on Chemical Safety (IPCS). 1997. International Chemical Safety Card on n-Heptane. (April 1997). Available from, as of February 2, 2015: http://www.inchem.org/documents/icsc/icsc/eics0657.htm

Lock EA. 1990. Chronic nephrotoxicity of 2,2,4-trimethylpentane and other branched-chain hydrocarbons. Toxicol Letters 53: 75-80.

May J. 1966. An odor evaluation apparatus for field and laboratory use. Am Ind Hyg Assoc J,

Meulenberg CJW, HPM Vijverberg. 2000. Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol Appl Pharmacol 165: 206–216.

Mullin LS, AW Ader, WC Daughtrey et al. 1990. Toxicology Update: Isoparaffinic hydrocarbons: A summary of physical properties, toxicity studies and human exposure data. J Appl Toxicol 10(2):135-142.

Organisation for Economic Co-operation and Development (OECD). 2010. SIDS Initial Assessment Profile. Category: C7-C9 Aliphatic Hydrocarbon Solvents. SIAM 30, 20-22 April 2010, US/ICCA. Available from: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=f7e12987-32ee-4f07-873f-df6402e9fd1b

Patty FA, WP Yant. 1929. Odor intensity and symptoms produced by commercial propane, butane, pentane, hexane, and heptanes vapor. Report of Investigations No. 2979. Department of Commerce, US Bureau of Mines.

Perbellini L, F Brugnone, D Caretta et al. 1985. Partition coefficients of some industrial aliphatic hydrocarbons (C5-C7) in blood and human tissues. *Brit J Ind Med* 42:162-167

Simonsen L and Lund S (1995). Four weeks inhalation exposure to n-heptane causes loss of auditory sensitivity in rats. Pharmacol. Toxicol. 76, 41-46

Swann HE, Jr., BK Kwon, GK Hogan et al. 1974. Acute inhalation toxicology of volatile hydrocarbons. Am Ind Hyg Assoc J 35(9): 511-518.

Takeuchi Y, Y Ono, N Hisanaga et al. 1980. A comparative study on the neurotoxicity of n-pentane, n-hexane, and n-heptane in the rat. Br J Ind Med 37 (3): 241-247.

Texas Commission on Environmental Quality (TCEQ). 2015a. Guidelines to develop toxicity factors. Chief Engineer's Office. RG-442. Available from: http://www.tceq.state.tx.us/implementation/tox/esl/guidelines/about.html

Texas Commission on Environmental Quality (TCEQ). 2015b. Approaches to derive odor-based values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

United States Environmental Protection Agency (USEPA). 1989. Health And Environmental Effects Document for n-Heptane. Final Draft ECAO-CIN-GO77 Washington, DC.

United States Environmental Protection Agency (USEPA). 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B. Risk Assessment Forum, Washington, DC.

U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on n-Heptane (142-82-5). Available from, as of February 2, 2016: http://www.epa.gov/iris/