Development Support Document
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Octane, All Isomers

CAS Registry Number:

Octane: 111-65-9

2,2,4-Trimethylpentane (Isooctane): 540-84-1

Other 16 Isomers

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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
TMP	2,2,4-trimethylpentane or isooctane
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
VEP	Visual evoked potential

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 two isomers of octane (n-octane and isooctane). 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-octane (hereafter octane) and 2,2,4-trimethylpentane (hereafter isooctane).

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

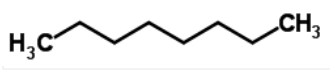
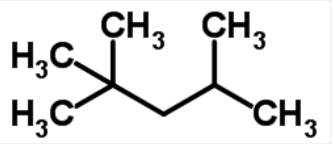
Short-Term Values	Concentration	Notes
Acute ReV [1-h]	19,000 µg/m^3 (4,100 ppb) **for octane, isooctane and 16 isomers**	**Critical Effect:** Transient neurobehavioral impairments in mice, and neurological function impairments in rats
$^{acute}ESL_{odor}$	---	Gasoline-like odor, not pungent or disagreeable
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	1,800 µg/m^3 (390 ppb) **for octane, isooctane, and 16 isomers**	**Critical Effect:** Free-standing NOAEL due to lack of general systemic 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)	5,600 µg/m^3 (1,200 ppb)[a] **for octane, isooctane and 16 isomers** **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Transient neurobehavioral impairments in mice, and neurological function impairments in rats
$^{acute}ESL_{odor}$	---	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)	540 µg/m^3 (120 ppb)[b] **for octane, isooctane and 16 isomers** **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Free-standing NOAEL due to lack of general systemic effects observed in rats in key study
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Inadequate information to assess carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 19,000 µg/m^3 (4,100 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.
[b] Based on the chronic ReV of 1,800 µg/m^3 (390 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

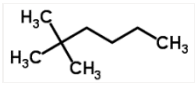
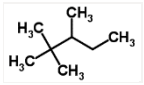
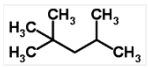
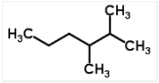
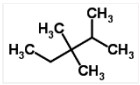
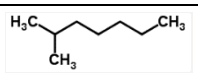
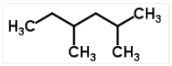
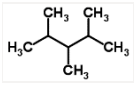
Table 3 Chemical and Physical Data

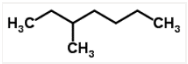
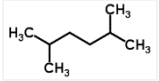
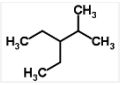
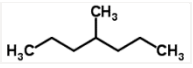
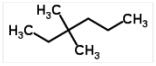
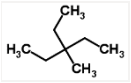
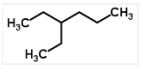
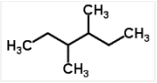
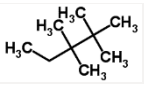
Parameter	Octane	Isooctane	Reference
Chemical Structure			ChemSpider
Molecular Weight	114.22	114.22	ACGIH (2001)
Molecular Formula	C_8H_{18}	C_8H_{18}	ACGIH (2001)
Structural Formula	CH_3-$(CH_2)_6$- CH_3	CH_3-$C(CH_3)_2$-CH_2-$CH(CH_3)$-CH_3	ACGIH (2001)
Physical State	Liquid	Liquid	ACGIH (2001)
Color	Colorless	Colorless	ACGIH (2001)
Odor	Gasoline-like odor	Gasoline-like odor	ACGIH (2001)
CAS Registry Number	111-65-9	540-84-1	ACGIH (2001)
Synonyms/Trade Names	n-Octane, C8 alkane	2,2,4-Trimethylpentane; isobutyltrimethylmethane	ACGIH (2001)
Solubility in water @ 25°C	Insoluble (0.66 mg/L)	Insoluble (2.44 mg/L)	OECD (2010)
Log K_{ow}	5.2	4.1	OECD (2010)
Vapor Pressure @ 25°C	18.8 mm Hg	65.7 mm Hg	OECD (2010)
Vapor density (air = 1)	3.94	3.9	IPCS (1993)
Density/Specific Gravity (water = 1)	0.7025 @ 20°C	0.6919 @ 20°C	ACGIH (2001)
Melting Point	-56.8°C	-116°C	ACGIH (2001)
Boiling Point	125.7°C	99.2°C	ACGIH (2001)
Lower Explosive Limit (LEL)	0.96%	1.1%	ACGIH (2001)
Conversion Factors	1 ppm = 4.67 mg/m^3 1 mg/m^3 = 0.24 ppm	1 ppm = 4.67 mg/m^3 1 mg/m^3 = 0.24 ppm	ACGIH (2001)

Chapter 2 Major Sources and Uses

The isomers of octane are colorless, flammable liquids with a characteristic gasoline-like odor. There are 18 isomers of octane including octane and isooctane (Table 4).

Table 4 Isomers of Octane and CAS No.

Isomer Name	CAS No.	Chemical Structure
Octane	111-65-9	
2,2-dimethylhexane	590-73-8	
2,2,3-trimethylpentane	564-02-3	
2,2,4-trimethylpentane	540-84-1	
2,3-dimethylhexane	584-94-1	
2,3,3-trimethylpentane	560-21-4	
2-methylheptane	592-27-8	
2,4-dimethylhexane	589-43-5	
2,3,4-trimethylpentane	565-75-3	

Isomer Name	CAS No.	Chemical Structure
3-methylheptane	589-81-1	
2,5-dimethylhexane	592-13-2	
3-ethyl-2-methylpentane	609-26-7	
4-methylheptane	589-53-7	
3,3-dimethylhexane	563-16-6	
3-ethyl-3-methylpentane	1067-08-9	
3-ethylhexane	619-99-8	
3,4-dimethylhexane	583-48-2	
2,2,3,3-tetramethylbutane	594-82-1	

Octanes are natural constituents in the paraffin fraction of crude oil and natural gas. The octane component in gasoline is a mixture of various octane isomers. Octane is used as a solvent and thinner, and in organic synthesis. Isooctane is also synthesized from the catalytic hydrogenation of trimethylpentene with a nickel catalyst. Isooctane has been used to add “high octane” or antiknock qualities to gasoline and aviation fuel (ACGIH, USEPA 2006). USEPA reports the production volume for the year 2005 were 450-4,500 and 45,000-225,000 metric tons for octane and isooctane, respectively (OECD 2010).

Octane 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 octanes into the atmosphere. The Hazardous Substance Databank

(HSDB 2013) reports that the average daily ambient concentration of octane in the United States was found to be 2.6 parts per billion (ppb).

In Texas, the highest reported 1-hour (h) concentration (from 2013 through 2014) of octane was 36.19 ppb collected from automated gas chromatograph (AutoGC) samples at an ambient air monitoring site at Corpus Christi Palm, Texas. The corresponding annual average concentrations were 0.05 and 0.03 ppb, respectively, in 2013 and 2014. The highest 24-h value of octane monitored in Texas was 59 ppb which was monitored in 2000. Form 2013-2014, the highest reported concentration (at an ambient air monitoring site at Denton Airport, Texas that collects 24-h canister samples every sixth day) was 11.15 ppb. The annual average concentrations of octane measured at the Denton Airport monitor in 2013 and 2014 were 0.22 and 0.31 ppb, respectively.

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

While the chemical properties vary slightly from isomer to isomer, every octane isomer has similar chemical-structure activities. Octane and isooctane are the two most common isomers of octane (ACGIH 2001). The main chemical and physical properties of these two isomers are summarized in Table 3. The other 16 isomers are of intermediate volatility between octane and isooctane (ACGIH 2001).

3.2 Health-Based Acute 1-Hour ReV and ESL

Octane has a low order of acute toxicity. Information from human studies regarding the acute toxicity of octanes is limited and insufficient for the development of the ReV and ESL. Therefore, animal studies were used to develop the acute ReV and ESL. Acute effects are considered similar to that of other saturated aliphatic hydrocarbons of similar length (C_3-C_8) (HSDB 2013). Short-term inhalation of high concentrations (≥ 1,000 ppm) of octane causes depression of the central nervous system (CNS), respiratory arrest, and mucous membrane, sensory and motor irritation in mice and rats (Glowa 1991, Swann et al. 1974, Stadler and Kennedy 1996, Boyes et al. 2010, Lammer et al. 2011). Schaper (1993) reported that the 50% depression in respiratory rate (RD_{50}) for octane in mice is 18,150 ppm. Stadler and Kennedy (1996) reported that the RD_{50} for isooctane in mice is much greater than 1,000 ppm. The narcotic effect of octane and isooctane in animals was observed at 6,600-13,700 ppm (Fuhner 1921, as cited in ACGIH 2001) and 9,000-10,000 ppm (Low 1987, as cited in El-Masri et al. 2009).

However, few studies have provided dose-response data to identify a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL). Animal studies that investigated octane or isooctane including Glowa (1991), Swann et al. (1974), Boyes et al. (2010), and Lammer et al. (2011) have provided the NOAEL and/or LOAEL values used to develop the acute ReV and ESL. The TCEQ chose Glowa (1991) and Boyes et al. (2011) as the

key studies, respectively, for octane and isooctane because both were well-conducted studies. Other animal studies were used as supporting studies.

3.2.1 Octane

3.2.1.1 Key Animal Study (Glowa 1991)

Glowa (1991) examined the ability of individual n-alkanes (C_5-C_8), including octane, 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).

For neurobehavioral 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 octane concentrations. Recovery was determined 30 min following removal from exposure. Concentration was increased from 100 ppm (nominal concentrations) until the response was abolished. The results showed that concentrations greater than 1,000 ppm octane decreased rate of response in a concentration-related manner with 3,000 ppm decreasing rate of response slightly more than 50%, and completely abolishing it (100%) at 5,600 ppm. Following exposures of 10,000 ppm, mice were observed to be engaged in circular locomotive activity. Response recovered to 15% of control levels 30 min following ceasing exposure to 10,000 ppm octane. Mean concentrations (± standard deviation) resulting in a 50% and 10% rate of response-decreasing potency (EC_{50} and EC_{10}) were 2,474 ± 496 and 1,508 ± 543 ppm, respectively. The level of 1,000 and 1,508 ppm (EC_{10}) can be considered a NOAEL and minimal LOAEL, respectively, for transient behavioral impairment.

For neuroendocrine effects assessment, the effect on HPA axis activation was studied by measuring adrenocortocotropin (ACTH) levels following exposure of mice (6 mice per concentration) to octane (100 to 10,000 ppm) for 30 min. Immediately after exposure ceased, animals were sacrificed and the ACTH levels in serum were measured. ACTH levels were the same from 100 to 3,000 ppm compared to the control. ACTH levels increased sharply (approximately 1,900% of control) at 10,000 ppm. However, no statistical analyses was 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 NOAEL of 1,000 ppm for transient behavioral impairment was conservatively used as point of departure (POD) to develop the acute ReV for octane.

3.2.1.2 Supporting Animal Studies

3.2.1.2.1 Lammers et al. (2011)

In a study by Lammers et al. (2011), neurobehavioral effects of acute exposure to C_5-C_{10} n-paraffins in rats were assessed in accordance with good laboratory practice (GLP) conditions. Male WAG/RijCHBR rats (8 rats/group) were exposed to air (control), 1,400, 4,200, or 14,000 mg/m^3 (corresponding to 0, 336, 1,008, 3,360 ppm, respectively) octane (99.3% purity, target concentrations) for 8 h/day (d) for 3 d. The mean analytical exposure concentrations were 1,405, 4,248, and 14,002 mg/m^3. Motor activity and neurobehavioral function (using a standardized functional observational battery (FOB)) were evaluated. The results showed that exposure to octane did not induce any dose-related effects on FOB or motor activity measures. There was an observation of slight gait alterations (not statistically significant) in the 14,000 mg/m^3 exposure group but only after the first 8-h exposure. In another study, separate groups of rats were evaluated for cognitive performance using a discrete-trial, two-choice visual discrimination performance testing. The results showed no treatment-related visual discrimination performance effects at exposure levels up to 14,000 mg/m^3 octane. In both studies, no changes in body weights or remarkable clinical signs between the groups were reported. The level of 14,000 mg/m^3 (or 3,360 ppm) was judged by the investigators to be a NOAEL for neurobehavioral effects and is approximately two times higher than the mild LOAEL of 1,500 ppm identified by Glowa et al. (1991). The NOAEL of 3,360 ppm supports the use of a NOAEL of 1,000 ppm identified by Glowa (1991) as a POD.

3.2.1.2.2 Sung et al. (2010)

Groups of specific-pathogen-free (SPF) Fisher 344 rats (5 rats/sex/group) were exposed to octane concentrations of 0, 500, 2,500, and 5,000 ppm (target concentrations) for 4 h. The acute inhalation toxicity test was performed according to the Organization for Economic Co-operation and Development (OECD) guidelines TG 403. No major toxicology-related abnormal changes such as changes in body weight or necropsy finds were evident, with the exception of a nervous system-related lethargy after 4 h in rats exposed to 5,000 ppm. However, recovery was considered complete after 18 h. None of the rats died. The levels of 2,500 and 5,000 ppm can be considered a NOAEL and minimal LOAEL for clinical symptoms.

3.2.1.3 Mode of Action (MOA) Analysis and Dose Metric

Octane is readily absorbed and distributed throughout the body and is excreted in the urine and expired air as CO_2. Octane is metabolized to hydroxy derivatives via a cytochrome p450 oxidase system. The 1-octanol formed is conjugated with glucuronic acid or undergoes further oxidation to octanoic acid.

The MOA for neurotoxic effects is attributed to alkanes' neurotoxic metabolite – diketones. 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.

3.2.1.4 POD and Critical Effect

For octane, the acute NOAEL of 1,000 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.

3.2.1.5 Dosimetric Adjustments

3.2.1.5.1 Exposure Duration Adjustments

The POD of 1,000 ppm was adjusted from 30-min exposure to 60-min (1-h) exposure concentration using Haber's rule as modified by ten Berge (1986) (TCEQ 2015a).

$$POD_{ADJ} = C_2 = (C_1) \times (T_1 / T_2)$$
$$= (1{,}000 \text{ ppm}) \times (30 \text{ min} / 60 \text{ min})$$
$$= 500 \text{ ppm}$$

3.2.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Octane is practically water insoluble. Acute exposures to octane cause transient behavioral impairment and neurological function impairment, respectively, which are systemic effects. In addition, toxicokinetic data on octane indicate that n-octane is rapidly absorbed via the lungs and widely distributed within the body. Octane 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 10.2 and 7.53 which were reported by Meulenberg and Vijverberg (2000). The ratio of the animal-to-human partition coefficients ($(H_{b/g})_A$ /($(H_{b/g})_H$)) is the regional gas dose ratio (RGDR) (TCEQ 2015a). The resulting POD_{HEC} from the POD_{ADJ} of 500 ppm in the Glowa (1991) rat study is:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$
$$= 500 \text{ ppm} \times [7.53 / 10.2]$$
$$= 500 \text{ ppm} \times 0.738$$
$$= 369.1176 \text{ ppm}$$

3.2.1.6 Adjustments of the POD_{HEC}

The POD_{HEC} of 369.1176 ppm was used to derive the acute ReV and ^{acute}ESL for octane. The following UFs were applied to the POD_{HEC} (Total UF = 90):

- 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, and
- a UF_D of 3 was used for uncertainty associated with an incomplete database. Animal studies were conducted for different toxicity endpoints including reproductive/developmental effects, and multiple animal species were used in inhalation bioassays. However, a value of 6 was not used because human studies for pure n-octane were not available, the endpoints evaluated in animals predominately concerned neurotoxicity, and a study evaluating developmental toxicity was only available in one species for isooctane. Consistent with TCEQ (2015a), confidence in the database is considered medium-high. The quality of the key rat study is high.

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 369.1176 \text{ ppm} / (10 \times 3 \times 3)$$
$$= 4.1013 \text{ ppm}$$
$$= 4{,}100 \text{ ppb (rounded to two significant figures)}$$

3.2.2 Isooctane

3.2.2.1 Key Animal Study (Boyes et al. 2010)

Boyes et al. (2010) evaluated the potential neurological impairment from acute inhalation exposure to isooctane in adult male Long-Evans rats using electrophysiological and behavioral assessments. In the electrophysiological assessments, rats (7-10 rats/group) were exposed (head-only) to 0, 500, or 1,000 ppm isooctane vapors (nominal concentrations) for 60 min. Visual evoked potentials (VEPs) were recorded from rats viewing modulated visual patterns before and at 10 min intervals during exposure and also for 60 min after exposure terminated. The spectral amplitude was measured at the rate of the visual pattern modulation (F1) and twice that stimulus rate (F2). All F2 amplitude values were expressed as a percentage of pre-exposure baseline values. The waveforms of rats in the control group were relatively stable and maintained a consistent sinusoidal shape over the course of the experiment. The waveforms of rats exposed to 1,000 ppm TMP for 60 min showed a progressive amplitude reduction and a general disruption of the characteristics continued to degrade over the following 60 min of clean air exposure. The F2 amplitude of the control group was declined slightly over time, but was reduced in the group exposed to1,000 ppm during the exposure session. There was no apparent recovery of F2 amplitude 60 min after the termination of isooctane exposure. Data analysis showed that the dose-response was not statistically significant. However, the repeated measure analysis showed a statistically significant dose-time interaction on F2 amplitude. Follow-up Turkey tests showed

statistically significant dose-related differences ($p < 0.05$) at the end of 60-min exposure session (i.e., time = 60 min) for 0 ppm vs. 1,000 ppm and 500 ppm vs. 1,000 ppm, but not for 0 ppm vs. 500 ppm. The 500 ppm and 1,000 ppm are conservatively considered the NOAEL and LOAEL values, respectively, for alterations of VEPs.

In behavioral assessments, 14 rats performed an appetitively motivated visual signal detection task while breathing 0, 500, 1,000, 1,500, 2,000, or 2,500 ppm isooctane for 62 min. Significant reductions in accuracy of performance were observed at the 2,500 ppm concentration when compared to the 0 ppm control animals. A NOAEL and LOAEL of 2,000 and 2,500 ppm for behavioral effects, respectively, were identified.

The lower NOAEL of 500 ppm for neurological function impairments was conservatively used as the POD to develop the acute ReV for TMP (isooctane).

3.2.2.2 Supporting Animal Studies

3.2.2.2.1 Swann et al. (1974)

Swann et al. (1974) studied the respiratory irritating properties of isooctane (99% pure) in male Swiss mice (25 g). Four animals were exposed head-only for 5 min at each of the following concentrations of isooctane: 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 isooctane. Concentrations less than 16,000 ppm produced no measurable irritation. At 16,000 ppm, there was sensory and motor irritation throughout the exposure, and 1/4 of the mice had sudden respiratory arrest. At 32,000 ppm, there was considerable sensory and motor irritation and irregular respiration, and all of the mice stopped breathing within 4 min of the onset of exposure. No apparent anesthesia was noted at any exposure concentration. 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 and the NOAEL for neurological function impairments is much lower, the NOAEL was not used as a POD to develop the acute ReV and ^{acute}ESL.

3.2.2.2.2 Stadler and Kennedy, Jr. (1996)

Stadler and Kennedy, Jr. (1996) evaluated the sensory irritation potential of a number of volatile organic chemicals that were identified in carpet emissions, including isooctane. Toxicity was evaluated for changes in respiratory function parameters by measuring the airborne concentration required to elicit an RD50 in Swiss-Webster mice. The mice were exposed to 30- min pure isooctane vapor at ≥ 1,000 ppm by inhalation. General signs of toxicity, respiratory rate decreases, and breathing patterns of respiratory irritation in the mice were not noted. The investigators concluded that the exhibited RD_{50} value for isooctane was much greater than 1,000 ppm. The RD_{50} of > 1,000 ppm supports the NOAEL of 500 ppm for isooctane-induced neurological impairment identified from the Boyes et al. (2010) key study.

3.2.2.2.3 Exxon (1987) Isooctane Studies

An acute inhalation toxicity study for isooctane was performed by Bio/dynamics Inc. on behalf of Exxon Corporation in 1978 and submitted to USEPA in 1987 (Exxon 1987), male and female SD rats, CD-1 mice, and Hartley guinea pigs (10/group) were exposed to 8,322 ppm (39,630 mg/m^3) isooctane for up to 4 h. No abnormal signs were seen in the rats after 15 min of exposure; however, after 20 min, convulsions were seen in most animals and two rats died within 30 min of the exposure. Convulsions, excessive lacrimation and salivation, and labored breathing were reported in the surviving rats, and all rats were dead within 55 min of the start of the exposure. In the mice, one animal died after 20 min and all the mice were dead within 75 min of exposure. Death occurred in 8/10 guinea pigs between 60 and 120 min of the exposure. At necropsy, lung discoloration was observed in all of the animals, and liver and kidney discoloration was observed in 2/10 of the animals.

In a separate testing performed by Bio/dynamics Inc., male and female SD rats (6 rats/group/sex) were exposed to 0, or a nominal concentration of 21,250 mg/m^3 (actual = 21,000 mg/m^3 or 4,504 ppm) Isopar C (85% isooctane) for 4 h. Mean animal body weights for the control and dose rats were comparable and unremarkable. A few exposed rats (3/12) exhibit signs of slight irritation. After Day 2 post-exposure, all signs of irritation abated. Observations performed at necropsy (Day 14 post-exposure) revealed low incidences of lung discoloration and dilated renal pelves in both the control (5/12) and exposure (4/12) groups. None of these observations were considered to be related to isooctane. The level of 4,504 ppm can be considered a LOAEL for slight irritation.

3.2.2.3 Mode of Action (MOA) Analysis and Dose Metric

Isooctane is less rapidly metabolized than octane to a range of metabolites that are excreted in the urine. Respiration is the most likely route by which isooctane is absorbed. Metabolism of isooctane probably occurs by omega and omega-l oxidation to yield the corresponding alcohol and acid metabolites. Elimination isooctane occurs mainly by metabolism to water-soluble products which are excreted in the urine and by exhalation of parent material (Dahl 1989).

The MOA for neurotoxic effects is attributed to diketones, the neurotoxic metabolite of alkanes. 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 was used as the dose metric.

3.2.2.4 POD and Critical Effect

For isooctane, the acute NOAEL of 500 ppm based on a 60-min inhalation rat study (Boyes et al. 2010) was used as the POD to develop the acute ReV for TMP (isooctane). The critical effect was neurological function impairment.

3.2.2.5 Dosimetric Adjustments

3.2.2.5.1 Exposure Duration Adjustments

Since the exposure duration for the NOAEL of 500 ppm identified from the Boyes et al. (2010) study included 60-min (1-h) exposure, there is no adjustment from exposure duration to 1-h. Thus, the POD was directly used as a POD_{ADJ}.

3.2.2.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Isooctane is practically water insoluble. Acute exposures to isooctane cause transient behavioral impairment and neurological function impairment, respectively, which are systemic effects. In addition, toxicokinetic data on isooctane indicate that isooctane is rapidly absorbed via the lungs and widely distributed within the body. Isooctane was therefore considered a Category 3 gas (USEPA 1994).

The measured $(H_{b/g})_A$ and $(H_{b/g})_H$ for isooctane are not available, since isooctane is similar to octane, the value of $(H_{b/g})_A/(H_{b/g})_H$) for octane was used used as the dosimetric adjustment factor (DAF) (Section 3.2.2.5.2) . The resulting subacute POD_{HEC} is

$POD_{HEC} = POD_{ADJ} \times 0.738 = 500 \text{ ppm} \times 0.738 = 369 \text{ ppm}$

3.2.2.6 Adjustments of the POD_{HEC}

The POD_{HEC} of 369 ppm was used to derive the acute ReV and ^{acute}ESL for isooctane. The following UFs were applied to the POD_{HEC} (Total UF = 90):

- a UF_H 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, and
- a UF_D of 3 was used for uncertainty associated with an incomplete database. Animal studies were conducted for different toxicity endpoints including reproductive/developmental effects, and multiple animal species were used in inhalation bioassays. However, a value of 6 was not used because the endpoints evaluated in animals were predominately limited to neurotoxicity and irritation, and a study evaluating developmental toxicity was only available in one species. Confidence in the database is considered medium-high, consistent with TCEQ (2015a). The quality of the key rat study is high.

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 369 \text{ ppm} / (10 \times 3 \times 3)$$
$$= 4.1 \text{ ppm}$$
$$= 4{,}100 \text{ ppb (rounded to two significant figures)}$$

3.2.3 Reproductive/Developmental Toxicity Studies

No information on the potential of octane to cause developmental toxicity in humans 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, respectively, 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 concentrations up to 1,200 ppm in an inhalation study. Isopar C also 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.

3.2.4 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 1,200 ppb (5,600 µg/m^3) for octane and isooctane is based on the acute ReV of 4,100 ppb (19,000 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 octane and isooctane.

Table 5 Summary of Acute ReV and ^{acute}ESL for Octane and Isooctane

Parameter	Octane	Isooctane
Study	Glowa (1991)	Boyes et al. (2010)
Study Quality	High	High
Study Population	adult male CD-1 mice (4-6 mice/group)	Long-Evans rats (7-10 rats/group)
Exposure Method	Incrementally increasing exposure inhalation from 100 ppm up to 10,000 ppm	Inhalation exposure to 0, 500, or 1,000 ppm
Exposure Duration	30 min	60 min
Critical Effects	Transient behavioral impairment at >1,000, 3,000, 5,600, 10,000 ppm	Neurological function impairments at 1,000 ppm
POD	1,000 ppm (NOAEL)	500 ppm (NOAEL)
POD_{ADJ} to 1h	500 ppm	500 ppm
POD_{HEC}	369 ppm	369 ppm
Total UFs	90	90
Intraspecies UF	10	10
Interspecies UF	3	3
Incomplete Database UF Database Quality	3 Medium to High	3 Medium to High
Acute ReV [1 h] (HQ = 1)	**4,100 ppb (19,000 µg/m^3)**	**4,100 ppb (19,000 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**1,200 ppb (5,600 µg/m^3)**	**1,200 ppb (5,600 µg/m^3)**

3.3 Health-Based Acute 24-Hour ReV

3.3.1 Octane

Consistent with TCEQ Guidelines (TCEQ 2015a), the potential need for a 24-h ReV was evaluated. However, monitored 24-h concentrations of octane and isomers across Texas (TAMIS 2005-2015) were ≥ 7 times below the chronic ReV of 390 ppb. Therefore, a 24-h ReV is not needed and is not derived in this DSD.

3.3.2 Isooctane

No available acute or subacute studies using exposure duration of ≥ 6h are available for the derivation of 24-ReV (TCEQ 2015a).

3.4 Welfare-Based Acute ESLs

3.4.1 Odor Perception

Octane has a gasoline-like odor. Odor detection thresholds of 48 and 150 ppm for octane have been reported by Amoore and Hautala (1983) and May (1966) , respectively. No odor threshold value for isooctane was reported. Since octane and isooctane do not have a pungent or disagreeable odor, 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 octane, isooctane, and other isomers.

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

The acute evaluation resulted in the derivation of the following values for both octane and isooctane:

- Acute ReV = 19,000 µg/m^3 (4,100 ppb)
- ^{acute}ESL = 5,600 µg/m^3 (1,200 ppb)

For the evaluation of ambient air monitoring data, the acute ReV of 19,000 µg/m^3 (4,100 ppb) is used (Table 1). The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 5,600 µg/m^3 (1,200 ppb) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5.1 Other Octane Isomers

No acute toxicity data were available describing the potential acute toxicity of 16 other octane isomers. For the purpose of health effects evaluations for air permit applications and/or ambient air monitoring data, the acute ReV and ESL values of 19,000 and 5,600 µg/m^3 for octane will be used as surrogates.

3.6 Acute Inhalation Observed Adverse Effect Levels (IOAELs)

The acute inhalation observed adverse effect level (^{acute}IOAEL) of 1,100 ppm for octane was based on the minimal 30-min $LOAEL_{HEC}$ of 1,112 ppm (LOAEL x RGDR= 1508 ppm x 0.738) for transient behavioral impairment determined from the mouse study (Glowa 1991). The 60-min ^{acute}IOAEL of 1,000 ppm for isooctane was derived based on the $LOAEL_{HEC}$ of 738 ppm (LOAEL x RGDR = 1000 ppm x 0.738) for neurological function impairment determined from rat study (Boyes et al. 2010). No duration adjustments were made although animal-to-human

dosimetric adjustments were performed. Effects occurred in some animals and these ^{acute}IOAELs represent 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 ^{acute}IOAEL levels are provided for informational purposes only (TCEQ 2015a).

- Octane ^{acute}IOAEL = 5,100 mg/m^3 (1,100 ppm) (rounded to 2 significant figures)
- Isooctane ^{acute}IOAEL = 3,400 mg/m^3 (740 ppm)

The margin of exposure between the ^{acute}IOAEL and the acute ReV (4.1 ppm) for octane and isooctane is approximately a factor of 268 and 180, respectively.

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. 1980) or n-nonane (Carpenter et al. 1978), and in repeated dose oral studies with octane or n-nonane (OECD 2010). Neurotoxicity of alkanes is correlated with the rate of metabolism to potentially neurotoxic gamma diketones. There appears to be a very low rate of metabolism to gamma diketones for n-alkanes except for n-hexane and no such metabolism for isoalkanes (OECD 2010). The only generally significant 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). No chronic inhalation studies were found in the literature. Only one subchronic inhalation toxicity study each was reported for octane (Sung et al. 2010) and isooctane (Exxon 1987).

4.2.1 Octane

4.2.1.1 Key Animal Study (Sung et al. 2010)

Sung et al. (2010) conducted a subchronic inhalation toxicity study where groups of SPF Fischer 344 rats (10 rats/group/sex) were exposed to octane concentrations of 0, 930, 2,620, and 7,480 mg/m^3 (0, 200, 560 and 1,600 ppm, respectively, target concentrations) for 6 h/d, 5 d/week for 13 weeks. The subchronic inhalation toxicity test was performed according to the OECD guidelines TG 403. The octane concentrations of each exposure chamber were within the range of target concentrations, and were consistently maintained for each inhalation toxicity test. No significant

differences were observed in food consumption between the treated animals and the control group, except between rats exposed to 1,600 ppm exposure and control male animals. The authors, however, indicated that these changes were not related to octane dose and were within normal ranges. No significant dose-dependent body or organ weight, ophthalmologic, hematologic, or blood biochemical parameters changes were observed in male and female animals after 13 weeks of octane exposure. The authors concluded that the NOAEL for clinical and histopathological differences was determined to be 1,600 ppm. The free-standing subchronic NOAEL was used as the POD to derive chronic ReV for octane.

4.2.1.2 MOA Analysis and Dose Metric

The MOA analysis was not applicable due to lack of general non-carcinogenic systemic effects (free-standing NOAEL) observed in a subchronic animal study. Therefore, as a default, 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 was used as the default dose metric.

4.2.1.3 POD and Critical Effect

The subchronic free-standing NOAEL of 1,600 ppm based on a 13-week inhalation rat study (Sung et al. 2010) was used as the POD to develop the chronic ReV. The critical effect was absence of general systemic effects.

4.2.1.4 Dosimetric Adjustments

4.2.1.4.1 Exposure Duration Adjustments

The POD of 1,600 ppm was adjusted from a discontinuous exposure (6 h/d for 5 d/week) to continuous exposure concentration.

$$POD_{ADJ} = POD \times (D/24\ h) \times (F/7\ d)$$

where:

D = Exposure duration, h per day

F = Exposure frequency, days per week:

$$POD_{ADJ} = 1{,}600\ ppm \times (6/24) \times (5/7) = 285.714\ ppm$$

4.2.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Octane is practically water insoluble. The endpoints studied by Sung et al. (2010) were for systemic rather than POE effects. Octane was considered a Category 3 gas. As described in Section 3.2.2.5.2, the ratio of $((H_{b/g})_A /((H_{b/g})_H)$ is 0.738. The POD_{HEC} from the POD_{ADJ} of 285.714 ppm in the Sung et al. (2010) rat study is:

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

= 285.714 ppm x [7.53/10.2]
= 285.714 ppm x 0.738
= 210.924 ppm

4.2.1.5 Adjustments of the POD_{HEC}

The POD_{HEC} of 210.924 ppm was used to derive the chronic ReV and ^{chronic}ESL for octane. The following UFs were applied to the POD_{HEC} (Total UF = 540):

- 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_{Sub} of 3 was considered appropriate to account for the use of a subchronic study. In addition, since only a free-standing NOAEL was identified , the NOAEL may be conservative, and
- a UF_D of 6 was used because only one inhalation animal study in one species was available and used to evaluate toxicity (e.g., the study showed no dose-response relationship) and neurotoxicity (a sensitive endpoint for octanes) was not evaluated. 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 n-heptane and n-nonane, with toxicity similar to octane (OECD 2010. Confidence in the database is considered low, consistent with TCEQ (2015a). The quality of the key rat study, however, is high.

Chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)
= 210.924 ppm / (10 x 3 x 3 x 6)
= 0.3906 ppm
= 390 ppb (rounded to two significant figures)

4.2.2 Isooctane

4.2.2.1 Key Animal Study (Exxon 1987)

A subchronic inhalation toxicity study for Isopar C (85% isooctane) was performed by Bio/dynamics Inc. on behalf of Exxon Corporation in 1978 and submitted to USEPA in 1987 (Exxon 1987). Male and female SD rats (35/group/sex) were exposed to 0, 400, or 1,200 ppm (nominal concentrations) Isopar C (85% isooctane) for 6 h/d, 5 d/week for 12 weeks. The analytical mean exposure concentrations for the low-dose and high-dose group were 385 and 1,180 ppm, respectively.

No treatment-related mortalities occurred in the study. With the exception of male rats exposed to 1,180 ppm, mean body weights for control and test animals were comparable and unremarkable. Mean body weights were significantly lower in males exposed to 1,180 ppm; however, the decreases in body weights were < 8% of the controls and were not considered

adverse effects. No statistically significant differences in clinical signs or hematological/microscopic parameters were observed. Compared to controls, an analysis of absolute and relative organ/body weight ratios indicated an increase in both absolute and relative mean kidney weights at both 385 and 1,180 ppm in males only. However, the results of kidney function tests were unremarkable. While the investigators consider changes in kidney weight to be treatment-related, increased kidney weights in male rats induced by isooctane may be related to α2μ-globulin accumulation in the proximal tubules, a low molecular weight protein found specifically in the urine of male rats (Short et al. 1989, USEPA 2007). However, α2μ-globulin accumulation or nephrotoxicity was not observed in male mice treated with isooctane (Lock 1990). Thus, like α2u-globulin associated nephropathy, increased kidney weights in male rats would not be considered isooctane-related effects. The level of 1,180 ppm was considered a free-standing NOAEL for body/organ weights changes and general systemic effects. The NOAEL of 1,180 ppm Isopar C (contains 85% isooctane) was conservatively used to derive the chronic ReV for isooctane.

4.2.2.2 Supporting Animal Study (Short et al. 1989)

Short et al. (1989) exposed male and female F344 rats to 50 ppm (234 mg/m^3) isooctane for 6 h/d, 5 d/week for 3 to 50 weeks. The only notable effects in this study were limited to the male rat kidney and consisted of an increase in α2u-globulin protein and hyaline droplet accumulation in the P2 segment of the proximal tubules, necrosis of the tubule epithelium, sustained regenerative tubule cell proliferation, and enhancement of CPN in male rats. None of these effects were observed in exposed female rats. The development of renal toxicity is related to the presence of α2u-globulin which occurs in the blood of male rats only (Dahl 1989). Since humans do not synthesize α2u-globulin, the nephrotoxicity observed in male rats is not considered relevant to human (Lock 1990, Mullin et al. 1990, OECD 2010). Therefore, the Short et al. (1989) subchronic study was not used to develop chronic toxicity factors for isooctane.

4.2.2.3 MOA Analysis and Dose Metric

The MOA analysis was not applicable due to lack of general non-carcinogenic systemic effects (free-standing NOAEL) observed in the subchronic animal study. Therefore, as a default, a threshold, nonlinear assessment was 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 was used as the default dose metric.

4.2.2.4 POD and Critical Effect

The subchronic free-standing NOAEL of 1,180 ppm based on a 12-week inhalation rat study (Exxon 1987) was used as the POD to develop the chronic ReV. The critical effect was absence of general systemic effects.

4.2.2.5 Dosimetric Adjustments

4.2.2.5.1 Exposure Duration Adjustments

The POD of 1,180 ppm was adjusted from a discontinuous exposure (6 h/d for 5 d/week) to continuous exposure concentration.

POD_{ADJ} = POD x (D/24 h) x (F/7 d)
= 1,180 ppm x (6/24) x (5/7) = 210.714 ppm

4.2.2.6 Default Dosimetry Adjustments from Animal-to-Human Exposure

Isooctane is practically water insoluble. The endpoints studied by Exxon (1987) were for systemic rather than POE effects. Isooctane was considered a Category 3 gas (Section 3.3.3.4.2). Since the measured $(Hb/g)_A$ and $(Hb/g)_H$ for isooctane are not available, a default value of one is used as the dosimetric adjustment factor (DAF) (i.e., $(H\ b/g)_A/(H\ b/g)_H$) (TCEQ 2015a). The resulting subacute POD_{HEC} is equal to the POD_{ADJ} of 210.714 ppm for isooctane.

4.2.2.7 Adjustments of the POD_{HEC}

The POD_{HEC} of 210.714 ppm was used to derive the chronic ReV and ^{acute}ESL for isooctane. The following UFs were applied to the POD_{HEC} (Total UF = 540):

- 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_{Sub} of 3 was considered appropriate to account for the use of a subchronic study. In addition, since only a free-standing NOAEL was identified , the NOAEL may be conservative, and
- a UF_D of 6 was used because only one inhalation animal study in one species was available and used to evaluate toxicity (e.g., the study showed no dose-response relationship) and neurotoxicity (a sensitive endpoint for octanes) was not evaluated. 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 n-heptane and n-nonane, with toxicity similar to octane (OECD 2010. However, additional information including subchronic neurotoxic and reproductive/developmental toxicity is available for other similar C_7-C_9 alkanes, e.g., for n-heptane and n-nonane (OECD 2010). Confidence in the database is considered low, consistent with TCEQ (2015a). The quality of the key rat study, however, is high.

Chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)
= 210.714 ppm / (10 x 3 x 3 x 6)
= 210.714 / 540
= 0.3902 ppm

= 390 ppb (rounded to two significant figures)

4.2.3 Summary of the Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

In deriving the chronic 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 $^{chronic}ESL_{threshold(nc)}$ of 120 ppb (540 µg/m^3) for octane is based on the chronic ReV of 390 ppb (1,800 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations.

- The $^{chronic}ESL_{threshold(nc)}$ of 120 ppb (540 µg/m^3) for isooctane is based on the chronic ReV of 390 ppb (1,800 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 octane and isooctane.

Table 6 Summary of Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for Octane and Isooctane

Parameter	Octane	Isooctane
Study	Sung et al. (2010)	Exxon (1987)
Study Quality	High	High
Study Population	Male and female Fisher 344 rats (10 rats/group/sex)	Male and female SD rats (35 rats/group/sex)
Exposure Method	0, 200, 560 and 1,600 ppm (target concentrations)	0, 385, or 1,180 ppm (analytical concentrations) Isopar C (85% isooctane)
Exposure Duration	6 h/d, 5 d/week for 13 weeks	6 h/d, 5 d/week for 12 weeks
Critical Effects	Absence of general systemic effects	Absence of body/organ weights changes and general systemic effects
POD	1,600 ppm (free-standing NOAEL)	1,180 ppm (free-standing NOAEL)
POD_{ADJ}	285.714 ppm	210.714 ppm
POD_{HEC}	210.856 ppm	210.714 ppm
Total UFs	540	540
Intraspecies UF	10	10
Interspecies UF	3	3
Subchronic UF	3	3
Incomplete Database UF *Database Quality*	6 Low	6 Low
Chronic ReV [1 h] (HQ = 1)	**390 ppb** **(1,800 µg/m^3)**	**390 ppb** **(1,800 µg/m^3)**
$^{chronic}ESL$ [1 h] (HQ = 0.3)	**120 ppb** **(540 µg/m^3)**	**120 ppb** **(540 µg/m^3)**

4.3 Carcinogenic Potential

No data were found on long-term carcinogenicity studies on octane or isooctane. The available studies showed that isooctane had a negative genotoxic potential, as isooctane did not increase

mutations at the TK locus, did not induce SCEs in a human lymphoblastoid cell line (Richardson et al. 1986, as cited by USEPA 2007) or DNA double-strand breaks in male rat kidney (McLaren et al. 1994, as cited by USEPA 2007), and did not stimulate UDS (unscheduled DNA synthesis) in isolated male rat or mouse hepatocytes (Loury et al. 1986, as cited by USEPA 2007).

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of octane, isooctane or other isomers. 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 octane and isooctane 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 octane. 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 octane or isooctane.

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

The chronic evaluation resulted in the derivation of the following values for both octane and isooctane:

- Chronic ReV = 1,800 µg/m^3 (390 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 540 µg/m^3 (120 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 1,800 µg/m^3 (390 ppb) is used (Table 1). The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{threshold(nc)}$ of 540 µg/m^3 (120 ppb) (Table 2). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5.1 Other Octane Isomers

No chronic toxicity data were available describing the potential chronic toxicity of 16 other octane isomers. For the purpose of health effects evaluations for air permit applications and/or ambient air monitoring data, the chronic ReV and ESL values of 1,800 and 540 µg/m^3 for isooctane will be used as surrogates

4.6 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)

The $^{chronic}IOAELs$ are derived based on $LOAEL_{HEC}$ values (TCEQ 2015a). Since subchronic/chronic LOAELs were not available for octane and isooctane, no $^{chronic}IOAEL$ values were derived.

Chapter 5 References

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