Development Support Document
Final, September 30, 2016

Nonane, All Isomers

CAS Registry Number:

n-Nonane: 111-84-2

Other 34 Isomers

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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
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
mm Hg	millimeters of mercury
HEC	human equivalent concentration

Acronyms and Abbreviations	Definition
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
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
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor

Acronyms and Abbreviations	Definition
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

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 nonane and all isomers. 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-nonane.

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

Short-Term Values	Concentration	Notes
Acute ReV [1-h]	16,000 µg/m^3 (3,000 ppb) **for n-nonane and 34 isomers**	**Critical Effect:** Decreases in CNS effects 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	1,500 µg/m^3 (290 ppb) **for n-nonane and 34 isomers**	**Critical Effect:** Decreases in body weight gains and CNS effects 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)	4,800 µg/m^3 (900 ppb)[a] **for n-nonane and 34 isomers** **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Decreases in CNS effects 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)	450 µg/m^3 (87 ppb)[b] **for n-nonane and 34 isomers** **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Decreases in body weight gains and CNS effects 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 1-h ReV of 16,000 µg/m^3 (3,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.
[b] Based on the chronic ReV of 1,500 µg/m^3 (290 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-Nonane	Reference
Chemical Structure		ChemIDPlus
Molecular Weight	128.26	ACGIH (2001)
Molecular Formula	C_9H_{20}	ACGIH (2001)
Structural Formula	CH_3-$(CH_2)_7$- CH_3	ACGIH (2001)
Physical State	Liquid	ACGIH (2001)
Color	Colorless	ACGIH (2001)
Odor	Gasoline-like odor	ACGIH (2001)
CAS Registry Number	111-84-2	ACGIH (2001)
Synonyms/Trade Names	Nonane	ACGIH (2001)
Solubility in water @ 25°C	Insoluble (0.220 mg/L @ 20°C)	HSDB (2016)
Log K_{ow}	5.65	HSDB (2016)
Vapor Pressure @ 25°C	4.45 mm Hg	HSDB (2016)
Vapor density (air = 1)	4.41	HSDB (2016)
Density/Specific Gravity (water = 1)	0.7174 @ 20°C	ACGIH (2001)
Melting Point	-53.5°C	ACGIH (2001)
Boiling Point	150.8°C	ACGIH (2001)
Lower Explosive Limit (LEL)	0.8%	ACGIH (2001)
Conversion Factors	1 ppm = 5.24 mg/m^3 1 mg/m^3 = 0.19 ppm	ACGIH (2001)

Chapter 2 Major Sources and Uses

Nonanes are major constituents of gasoline, VM&P naphtha and Stoddard solvents. Nonane is produced commercially by fractional distillation or refining of petroleum. Nonanes are used mainly as a component of the fuel source kerosene, in organic syntheses, and in biodegradable detergents (ACGIH 2001). Nonane is listed as a High Production Volume (HPV) chemical. The USEPA reports the production volume for the year 2005 was 225-450 metric tons for n-nonane (OECD 2010).

Nonanes are released in air primarily from evaporative emissions resulting from manufacturing or using products containing nonanes. The highest reported 24-hour (h) canister concentration of nonane of 3.43 ppb was reported during the 2005 to 2015 timeframe. This value was reported in Houston at the Deer Park monitor in 2011. In 2013 and 2014, an ambient air monitoring site at Denton Airport, Texas that collects 24-h n-nonane canister samples every sixth day measured the highest reported concentration in the state of 1.83 ppb. The 2013 and 2014 annual average concentrations at the Denton Airport monitor were both 0.05 ppb.

The isomers of nonane are colorless, highly flammable liquids with a gasoline-like odor and are practically insoluble in water. There are 35 isomers of nonane including n-nonane (Appendix).

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

While the chemical properties vary slightly from isomer to isomer, every nonane isomer has similar structure activities. The main chemical and physical properties of n-nonane are summarized in Table 3.

3.2 Health-Based Acute 1-Hour ReV and ESL

No human studies are available concerning the acute adverse effects of nonane. Two acute inhalation studies in animals were available concerning the adverse effects of nonane (Carpenter et al. 1978 and Nilsen et al. 1988). Like other C_7-C_9 aliphatic hydrocarbons, n-nonane has a low acute toxicity in experimental animals. Respiratory tract irritation and transient CNS depression were primarily observed at high concentrations. Acute effects in humans or animals are considered similar to that of other saturated aliphatic hydrocarbons of similar carbon chain length (C_7-C_9) (OECD 2010). The LC_{50} for male Harlan-Wistar rats (16/group) exposed to n-nonane for 4 h and held for 14 days (d) was 3,200 ppm (17,000 mg/m^3) (Carpenter et al. 1978). The other LC_{50} value of 4,467 ppm was identified in male Sprague Dawley (SD) rats exposed to n-nonane for 8 h and observed for 14 d post exposure (Nilsen et al. 1988). The Carpenter et al. (1978) study selected as the key study for derivation of the acute ReV and ^{acute}ESL.

3.2.1 Key Animal Study (Carpenter et al. 1978)

In a preliminary repeated inhalation study (Carpenter et al. 1978), 10 female Harlan-Wistar rats were exposed to a target concentration of 10 milligrams per liter (mg/L) of n-nonane 6 hours/day

(h/d) for 1 day (d), and were exposed for an additional 4 d at 6 h/d after resting over a weekend. The mean measured concentration for the total 7 d time period (including the weekend) was 8,100 mg/m^3 (1,500 ppm). Mild tremors, slight coordination loss, and slight irritation of the eyes and extremities were observed in rats during the next 4 d. A free-standing LOAEL of 1,500 ppm was identified.

After the preliminary subacute study, Carpenter et al. (1978) conducted a 13-week subchronic study in which groups of 25 male Harlan-Wistar rats were exposed to 0, 360, 590 and 1,600 ppm (0, 1,900, 3,100, and 8,400 mg/m^3, respectively) n-nonane for 6 h/d, 5 d/week for 13 weeks. Clinical signs such as salivation, mild coordination loss, and fine tremors were observed in rats exposed to 1,600 ppm throughout the first 4 d of exposure. No such signs of distress were observed in rats exposed to 360 and 590 ppm. The decreases in body weight gains in rats exposed to 1,600 ppm were statistically significant compared to the controls after 3, 17, 32, 46 and 61 d of exposure. A NOAEL and LOAEL of 590 and 1,600 ppm after 3 d of exposure for decreases in body weight gains were identified from this study. A NOAEL and LOAEL of 590 and 1,600 ppm for signs of distress throughout the first 4 d of exposure and for decreases in body weight gains after 3 d of exposure were identified from this study. The NOAEL of 590 ppm for signs of distress (e.g., mild coordination loss, fine tremors) observed throughout the first 4 d of exposure (presumable beginning on day one) was used as a point of departure (POD) to derive the acute ReV for n-nonane because the NOAEL identified in the only other available acute inhalation study (Nilsen et al. 1988) was higher than the LOAEL identified in Carpenter et al. (1978).

3.2.2 Supporting Animal Study (Nilsen et al. 1988)

In an acute lethal toxicity study by Nilsen et al. (1998), groups of 10 male SD rats were exposed to 2,414 ± 7, 3560 ± 17, 4,438 ± 319 and 5,280 ± 77 ppm (mean measured concentration ± standard deviation) n-nonane for 8 h and observed for the following 14 d. Four additional rats were exposed simultaneously to filtered air as the control group. Dose-response relationships were observed in mortality [0/10, 1/10, 4/10 and 9/10 from the lowest (2,414 ppm) to the highest (5,280 ppm) groups] and behavior changes during the 8 h exposure. Gross ataxia, general and focal seizure and spasms were observed in rats exposed to 3,560, 4,438 and 5,280 ppm. No toxic effects were observed in rats exposed to 2,414 ppm. The level of 2,414 ppm was considered a NOAEL for this study. However, signs of distress (e.g., mild coordination loss, fine tremors) occurred at a lower concentration (LOAEL of 1,600 pm) throughout the first 4 d of exposure in the key study of Carpenter et al. (1978).

3.2.3 Reproductive and Developmental Toxicity Studies

No information on the potential of nonane 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 n-nonane.

3.2.4 Mode of Action (MOA) Analysis and Dose Metric

n-Nonane is readily absorbed and distributed throughout the body and is excreted in the urine and expired air as CO_2. Nonane has an octanol:water partition coefficient (Log K_{ow}) of 5.65. It is metabolized to 2-nonanol by cytochrome P450 enzymes, and further to 2-nonanone by alcohol dehydrogenase (Robinson and Merrill 2007).

n-Nonane has been observed to distribute and accumulate preferentially into rat brain tissue. In a study of distribution and accumulation, Zahlsen et al. (1990 as cited in OECD 2010) reported that n-nonane has the highest accumulation potential in the brain with low concentrations in the blood. The measured blood:air and brain:air partition coefficients were 5.13 and 25.85, respectively, for rats exposed to n-nonane at 400 ppm (Robinson and Merrill 2007). The significant distribution in the brain of the n-nonane, clinical signs of cerebellar dysfunction and damage of cerebellar neurons would suggest that the CNS is a possible target organ for the toxic effects of the n-nonane. The MOA and potential for n-nonane-induced CNS effects is thought to involve/be proportional to the n-nonane concentration in the brain (OECD 2010). 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-nonane, the acute NOAEL of 590 ppm based on a 6 h/d, 5 d/week subchronic inhalation rat study (Carpenter et al. 1978) was used as the POD to develop the acute ReV, although it should be noted that the critical effects occurred throughout the first 4 d of exposure (presumably beginning on day one). The critical effects were CNS effects (e.g., mild coordination loss, fine tremors) observed throughout the first 4 d of exposure.

3.2.6 Dosimetric Adjustments

3.2.6.1 Exposure Duration Adjustments

The POD of 590 ppm from the Carpenter et al. (1978) study was adjusted from a 6-h exposure to a 1-h exposure concentration using Haber's rule as modified by ten Berge with a default value of "n"=3 (TCEQ 2015a).

$$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(590 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 1{,}072.10 \text{ ppm}$$

3.2.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

n-Nonane is practically water insoluble. Acute exposures to n-nonane cause CNS effects which are systemic effects and thus, n-nonane was considered a Category 3 gas (TCEQ 2015a). 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 the rat ($(H_{b/g})_A$ for n-nonane is 5.13 (Robinson and Merrill 2007). The measured blood/air partition coefficient in humans ($(H_{b/g})_H$) for n-nonane is not available. Since n-nonane is similar to n-octane, the value of $(H_{b/g})_H$ (10.2) for n-octane was used to calculate the dosimetric adjustment factor (DAF) (Section 3.2.2.5.2). The resulting POD_{HEC} from the POD_{ADJ} of 1,072.08 ppm in the Carpenter et al. (1978) rat study is:

$$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A / (H_{b/g})_H]$$
$$= 1{,}072.08 \text{ ppm} \times [5.13/10.2]$$
$$= 1{,}072.08 \text{ ppm} \times 0.503$$
$$= 539.20 \text{ ppm}$$

3.2.7 Adjustments of the POD_{HEC}

The POD_{HEC} of 539.193 ppm was used to derive the acute ReV and ^{acute}ESL for n-nonane. 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, and

- a UF_D of 6 was used for uncertainty associated with an incomplete database because one acute repeated animal inhalation study and one acute lethal toxicity studies were conducted in one animal species. 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_8 n-alkanes e.g., for n-heptane and n-octane. Consistent with TCEQ (2015a), confidence in the database is considered medium. The quality of the key rat study is medium to high.

Acute ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 539.20 ppm / (10 x 3 x 6)
= 2.996 ppm
= 3,000 ppb or 16,000 µg/m^3 (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 900 ppb (4,800 µg/m^3) for n-nonane is based on the acute ReV of 3,000 ppb (16,000 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 the acute ReV and ^{acute}ESL for n-nonane.

Table 4. Summary of Acute ReV and ^{acute}ESL for n-Nonane

Parameter	Values and Descriptions
Study	Carpenter et al. (1978)
Study Quality	Medium to high
Study Population	Harlan-Wistar rats (25/group)
Exposure Method	0, 360, 590 and 1,600 ppm
Exposure Duration	6 h/d for 4 d
Critical Effects	CNS effects
POD	590 ppm (NOAEL)
POD_{ADJ} to 1h	1,072.10 ppm
POD_{HEC}	539.20 ppm
Total UFs	180
Intraspecies UF	10
Interspecies UF	3
Incomplete Database UF *Database Quality*	6 Medium
Acute ReV [1 h] (HQ = 1)	**3,000 ppb (16,000 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**900 ppb (4,800 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, the highest monitored 24-h concentration of nonane and isomers (3.43 ppb) across Texas (TAMIS 2005-2015) was about 28 times below the chronic ReV of 98 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-Nonane has a gasoline-like odor. Odor detection thresholds of 47 ppm have been reported by Amoore and Hautala (1983). Since nonane and isomers 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 nonanes.

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

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

- Acute ReV = 16,000 µg/m^3 (3,000 ppb)
- ^{acute}ESL = 4,800 µg/m^3 (900 ppb)

For the evaluation of ambient air monitoring data, the acute ReV of 16,000 µg/m^3 (3,000 ppb) is used (Table 1). The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 4,800 µg/m^3 (900 ppb) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5.1 Other Nonane Isomers

No acute toxicity data were available describing the potential acute toxicity of 34 other nonane 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 16,000 and 4,800 µg/m^3 for n-nonane will be used as surrogates.

3.6 Acute Inhalation Observed Adverse Effect Levels (IOAELs)

The acute inhalation observed adverse effect level (^{acute}IOAEL) of 800 ppm for n-nonane was based on the 6-h $LOAEL_{HEC}$ of 800 ppm (LOAEL x RGDR= 1,600 ppm x 0.503) for transient CNS effects in rats (Carpenter et al. 1978). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. Effects occurred in some animals and the ^{acute}IOAEL represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The ^{acute}IOAEL level is provided for informational purposes only (TCEQ 2015a). The ^{acute}IOAEL for n-nonane is:

- n-Nonane ^{acute}IOAEL = 4,200 mg/m^3 (800 ppm) (rounded to 2 significant figures)

The margin of exposure between the ^{acute}IOAEL (800 ppm) and the acute ReV (3 ppm) for n-nonane is approximately a factor of 267.

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 such as neuropathy 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 n-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 CNS depression in some studies. CNS effects (signs of distress) generally occurred within the first few days of exposure to n-nonane and abated by the second week of study and these effects did not appear to worsen with longer exposures (Carpenter et al. 1978). No chronic inhalation studies were found in the literature. Only one subchronic inhalation toxicity study was reported for n-nonane (Carpenter et al. 1978). The Carpenter et al. (1978) 13-week subchronic inhalation study in rats was used as the key study to derive chronic toxicity factors.

4.2.1 Key Animal Study (Carpenter et al. 1978)

In the Carpenter et al. (1978) subchronic study, groups of 25 male Harlan-Wistar rats were exposed to 0, 360, 590 and 1,600 ppm n-nonane for 6 h/d, 5 d/week for 13-weeks. Three rats from each group were sacrificed for histopathological examination after 19- and 38-d intervals. Body weight changes were monitored after 4, 18, 33, 47 and 62 d of exposure. Micropathological examination of tissues and blood analyses were conducted after 4, 8 and 13 weeks of exposure. The results showed that no lesions of tissue and hematological findings were observed in all exposed rats after 4, 8, and 13 weeks of exposure. The blood serum glutamic pyruvic transaminase (SGPT) value from rats exposed to 1,600 ppm after 4 weeks, but not after 8 or 13 weeks, was statistically significant higher that of the controls. No statistically significant differences from the controls were observed in other clinical chemistry analyses after 4, 8 or 13 weeks. Clinical signs of distress such as salivation, mild coordination loss, and fine tremors were observed in rats exposed to 1,600 ppm throughout the entire 62 d of exposure. The signs of distress occurred within the first few days of exposure and that these effects did not appear to worsen with longer exposures. No such signs of distress were observed in rats exposed to 360 and 590 ppm. The decreases in body weight gains in rats exposed to 1,600 ppm were statistically significant compared to the controls after 4, 18, 33, 47 and 62 d. A NOAEL and LOAEL of 590 and 1,600 ppm for decreased body weight gain and signs of distress due to subchronic exposure were identified from this study. The NOAEL of 590 ppm for these effects was used as the POD to derive the chronic ReV for n-nonane.

4.2.2 Reproductive/Developmental Toxicity Studies

As described in Section 3.2.3, no information on the potential of nonane to cause reproductive/developmental toxicity in humans or animals is available. However, studies from exposures to C7-C8 n-alkanes indicated that n-alkanes (e.g., isooctane) do not cause reproductive/developmental effects. OECD (2010) conducted a weight-of-evidence (WOE)

analysis using available data from the inhalation reproductive/developmental toxicity studies from isooctane and other analogous substances. For example, no adverse reproductive/developmental effects were observed in rats exposed to 1,200 ppm Isopar C (contains 85% isooctane) or 8,000 ppm light alkylate naphtha analog (CAS RN 64741-66-8) (contains ~40% C_7-C_9 isoparaffins with the balance of paraffins in the C_5 range). The WOE analysis suggests that C_7-C_9 aliphatic hydrocarbons are unlikely to produce reproductive/developmental toxicity.

4.2.3 MOA Analysis and Dose Metric

n-Nonane is readily absorbed and distributed throughout the body and is excreted in the urine and expired air as CO_2. Nonane has an octanol:water partition coefficient (Log K_{ow}) of 5.65. It is metabolized to 2-nonanol by cytochrome P450 enzymes, and further to 2-nonane by alcohol dehydrogenase (Robinson and Merrill 2007).

As described in Section 3.2.1.3, the MOA and potential for n-nonane-induces CNS effects is thought to involve/be proportional to n-nonane concentration in the brain (OECD 2010). 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.

4.2.4 POD and Critical Effect

The subchronic NOAEL of 590 ppm based on a 13-week inhalation rat study (Carpenter et al. 1978) was used as the POD to develop the chronic ReV. The critical effects were decreased body weight gain and CNS effects, which are both considered general systemic effects.

4.2.5 Dosimetric Adjustments

4.2.4.1 Exposure Duration Adjustments

The POD of 590 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)

where:

D = Exposure duration, h per day

F = Exposure frequency, days per week:

POD_{ADJ} = 590 ppm x (6/24) x (5/7) = 105.357 ppm

4.2.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The endpoints studied by Carpenter et al. (1978) were for systemic rather than point of entry (POE) effects. n-Nonane was considered a Category 3 gas. As described in Section 3.6.1.2, the

ratio of $((H_{b/g})_A /((H_{b/g})_H)$ is 0.503. The POD_{HEC} from the POD_{ADJ} of 105.357 ppm in the Carpenter et al. (1978) rat study is:

$POD_{HEC} = POD_{ADJ} \times [(H_{b/g})_A /(H_{b/g})_H]$
$= 105.357 \text{ ppm} \times [5.13/10.2]$
$= 105.357 \text{ ppm} \times 0.503$
$= 52.995 \text{ ppm}$

4.2.6 Adjustments of the POD_{HEC}

The POD_{HEC} of 52.995 ppm was used to derive the chronic ReV and ^{chronic}ESL for n-nonane. 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_{Sub} of 1 was considered appropriate to account for the use of a subchronic study. A higher value was not used because CNS effects are generally expected to be more dependent on the attainment of critical blood concentrations. Like other n-alkanes, n-nonane is not expected to accumulate in tissues from intermittent inhalation exposures to low concentrations. The signs of distress occurred within the first few days of n-nonane exposure and that these effects did not appear to worsen with longer exposures. The NOAEL and LOAEL for decreased body weight gain and signs of distress were identical after the first 4 d and throughout 62 d of exposure), and
- a UF_D of 6 was used because only one subchronic inhalation animal study in one species was available and used to evaluate toxicity. A higher value of 10 was not used because additional information including subchronic neurotoxic and reproductive/developmental toxicity is available for similar C_7-C_8 alkanes, e.g., for n-heptane and n-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 $= POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D)$
$= 52.995 \text{ ppm} / (10 \times 3 \times 1 \times 6)$
$= 0.294 \text{ ppm}$
$= 290 \text{ ppb or } 1{,}500 \text{ µg/m}^3 \text{ (rounded to two significant figures)}$

4.2.7 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 87 ppb (450 µg/m^3) for n-nonane is based on the chronic ReV of 290 ppb (1,500 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 ReV and $^{chronic}ESL_{threshold(nc)}$ for n-nonane.

Table 5 Summary of Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for n-Nonane

Parameter	Values and Descriptions
Study	Carpenter et al. (1978)
Study Quality	Medium to high
Study Population	Harlan-Wistar rats (25/group)
Exposure Method	0, 360, 590 and 1,600 ppm
Exposure Duration	6 h/d, 5 d/week for 13 weeks
Critical Effects	Decrease in body weight gains, transient CNS effects
POD	590 ppm (NOAEL)
POD_{ADJ}	105.357 ppm
POD_{HEC}	52.995 ppm
Total UFs	180
Intraspecies UF	10
Interspecies UF	3
Subchronic to chronic extrapolation UF	1
Incomplete Database UF *Database Quality*	6 Low
Chronic ReV (HQ = 1)	**290 ppb (1,500 µg/m^3)**
$^{chronic}ESL$ (HQ = 0.3)	**87 ppb (450 µg/m^3)**

4.3 Carcinogenic Potential

No data were found on the carcinogenicity of n-nonane. n-Nonane was negative in the Ames Salmonella assay (ACGIH 2001). The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of nonane. The American Conference of Governmental Industrial Hygienists (ACGIH) has not assigned a carcinogenicity designation to this chemical. Thus, a $^{chronic}ESL_{nonthreshold(c)}$ cannot and 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 nonane.

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

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

- Chronic ReV = 1,500 µg/m^3 (290 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 450 µg/m^3 (87 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 1,500 µg/m^3 (290 ppb) is used (Table 1). The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{threshold(nc)}$ of 450 µg/m^3 (87 ppb) (Table 2). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5.1 Other Nonane Isomers

No chronic toxicity data were available describing the potential chronic toxicity of 34 other nonane 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 1,500 and 450 µg/m^3 for n-nonane will be used as surrogates.

4.6 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)

No chronic LOAEL was available to derive a chronic inhalation observed adverse effect level (^{chronic}IOAEL). However, for comparison purpose, a ^{subchronic}IOAEL of 800 ppm for n-nonane was derived based on the $LOAEL_{HEC}$ of 800 ppm (LOAEL x RGDR= 1,600 ppm x 0.503) for decreases in body weight gains from the subchronic rat study (Carpenter et al. 1978). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. Effects occurred in some animals and the ^{subchronic}IOAEL 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 ^{subhronic}IOAEL level is provided for informational purposes only (TCEQ 2015a). The ^{subchronic}IOAEL for n-nonane is:

- n-Nonane ^{subchronic}IOAEL = 4,200 mg/m^3 (800 ppm) (rounded to 2 significant figures)

Chapter 5 References

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Appendix Nonane Isomers

Table 6. Nonane Isormers and CAS No.

Name	CAS No.
n-nonane	111-84-2
2-methyloctane	3221-61-2
3-methyloctane	2216-33-3
4-methyloctane	2216-34-4
2,2-dimethylheptane	1071-26-7
2,3-dimethylheptane	3074-71-3
2,4-dimethylheptane	2213-23-2
2,5-dimethylheptane	2216-30-0
2,6-dimethylheptane	1072-05-5
3,3-dimethylheptane	4032-86-4
3,4-dimethylheptane	922-28-1
3,5-dimethylheptane	926-82-9
4,4-dimethylheptane	1068-19-5
3-ethylheptane	15869-80-4

Name	CAS No.
4-ethylheptane	2216-32-2
2,2,3-trimethylhexane	16747-25-4
2,2,4-trimethylhexane	16747-26-5
2,2,5-trimethylhexane	3522-94-9
2,3,3-trimethylhexane	16747-28-7
2,3,4-trimethylhexane	921-47-1
2,3,5-trimethylhexane	1069-53-0
2,4,4-trimethylhexane	16747-26-5
3,3,4-trimethylhexane	16747-31-2
3-ethyl-2-methylhexane	16789-46-1
4-ethyl-2-methylhexane	3074-75-7
3-ethyl-3-methylhexane	3074-76-8

Name	CAS No.
4-methyl-3-ethylhexane	3074-77-9
2,2,3,3-tetramethylpentane	7154-79-2
2,2,3,4-tetramethylpentane	1186-53-4
2,2,4,4-tetramethylpentane	1070-87-7
2,3,3,4-tetramethylpentane	16747-38-9
3-ethyl-2,2-dimethylpentane	16747-32-3
3-ethyl-2,3-dimethylpentane	16747-33-4
3-ethyl-2,4-dimethylpentane	1068-87-7
3,3-diethylpentane	1067-20-5