Hexane, All Isomers

CAS Registry Number:

n-Hexane: 110-54-3

Other 4 Isomers

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Development Support Document

Final, August 16, 2017

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

DSD History

Effective Date	Reason
October 15, 2007	Original n-Hexane DSD posted as final
September 14, 2015	The odor-based value was withdrawn because n-hexane does not have a pungent, disagreeable odor (TCEQ 2015b).
July 8, 2016	Public request for toxicity information on isomers of n-hexane
September 2, 2016	Public request for toxicity information on n-hexane
December 30, 2016	Hexane, All Isomers DSD proposed for public comment
August 16, 2017	Hexane, All Isomers DSD posted as final

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
AMCV	air monitoring comparison value
^{o}C	degrees Celsius
CNS	central nervous system
d	day(s)
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
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
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IOAEL	inhalation observed adverse effect level
^{acute}IOAEL	acute inhalation observed adverse effect level
^{subacute}IOAEL	subacute inhalation observed adverse effect level
^{chronic}IOAEL$_{(nc)}$	chronic inhalation observed adverse effect level (noncancer effects)
^{chronic}IOAEL$_{(c)}$	chronic inhalation observed adverse effect level (cancer effects)
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram
µg/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
ReV	reference value
Acute ReV	acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements

Acronyms and Abbreviations	Definition
Acute ReV-24hr	acute 24-hour health-based reference value for chemicals meeting minimum database requirements
Chronic $ReV_{threshold(nc)}$	chronic health-based reference value for threshold dose response noncancer effects
RGDR	regional gas dose ratio
RPF	relative potency factor
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
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
wk	week(s)
yr	year(s)

Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of n-hexane and all isomers, respectively, for use in air permitting and air monitoring. 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-hexane).

Table 1. Acute Health and Welfare-Based Screening Values for Hexane, All Isomers

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	19,000	5,500	M	A	--	Neuroendocrine effects in rats.	Applicable to n-hexane and 4 isomers.
Acute ReV-24hr	24 h	19,000	5,500	M	A	--	Reduction in fetal body weight in rats.	Applicable to n-hexane and 4 isomers; used for the evaluation of 24-h air monitoring data.
^{acute}ESL [a]	**1 h**	**5,600**	**1,600**	**P**	**S,D**	**--**	**Neuroendocrine effects in rats.**	**Applicable to n-hexane and 4 isomers.**
^{acute}IOAEL	20 h	3,500,000	1,000,000	N	none	--	Reduction in fetal body weight in rats.	--
^{subacute}IOAEL	--	--	--	--	--	--	--	--
$^{acute}ESL_{odor}$	--	--	--	--	--	--	--	Gasoline-like odor, not pungent or disagreeable.
$^{acute}ESL_{veg}$	--	--	--	--	--	--	--	No data found.

Bold values used for air permit reviews.

[a] Based on the acute 1-h ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2. Chronic Health and Welfare-Based Screening Values for Hexane, All Isomers

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Chronic $ReV_{threshold(nc)}$	70 yr	670	190	M	A	--	Peripheral neuropathy in occupational workers from an offset printing factory.	Applicable to n-hexane and 4 isomers.
$^{chronic}ESL_{threshold(nc)}$ [a]	**70 yr**	**200**	**57**	**P**	**S,D**	**--**	**Same as above.**	**Applicable to n-hexane and 4 isomers.**
$^{chronic}IOAEL_{(nc)}$	70 yr	460,000	130,000	N	none	--	Same as above.	--
$^{chronic}ESL_{threshold(c)}$	--	--	--	--	--	--	--	Inadequate information to assess carcinogenic potential.
$^{chronic}ESL_{nonthreshold(c)}$	--	--	--	--	--	--	--	Inadequate information to assess carcinogenic potential.
$^{chronic}IOAEL_{(c)}$	--	--	--	--	--	--	--	--
$^{chronic}ESL_{veg}$	--	--	--	--	--	--	--	No data found.
$^{chronic}ESL_{animal}$	--	--	--	--	--	--	--	No data found.

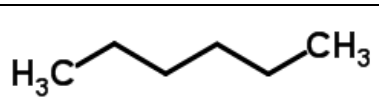
Bold values used for air permit reviews

[a] Based on the chronic ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

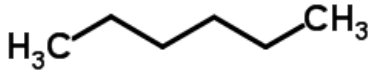
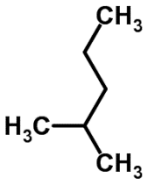
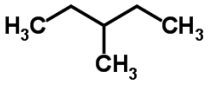
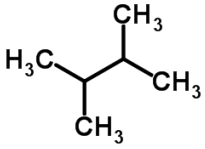
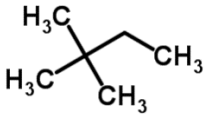
Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_6H_{14}	Chemfinder 2004
Chemical Structure		ChemSpider 2016
Molecular Weight	86.1766	TRRP 2006
Physical State	Liquid	TRRP 2006
Color	Colorless	Chemfinder 2004
Odor	Gasoline type	Chemfinder 2004
CAS Registry Number	110-54-3	TRRP 2006
Synonyms	n-Hexane, Hexane/mixed isomers, Hexanes, dipropyl, gettysolve-b, Hex, Hexyl hydride, Normal hexane, skellysolve B	Chemfinder 2004
Solubility in water, mg/L	13.0 mg/L	TRRP 2006
Log P_{ow} or K_{ow}	3.9	Chemfinder 2004
Vapor Pressure	153 mm Hg at 25°C	HSDB 2005
Relative Vapor Density	0.2 cm^2/s	TRRP 2006
Density	0.67 at 25°C	HSDB 2005
Melting Point	-95°C to -100°C	Chemfinder 2004
Boiling Point	69°C	Chemfinder 2004
Conversion Factors	1 $\mu g/m^3$ = 0.284 ppb 1 ppb = 3.52 $\mu g/m^3$	Toxicology Division

Chapter 2 Major Uses or Sources

n-Hexane and other isomers (hexanes) are all colorless volatile liquids at room temperature, odorless when pure, low solubility in water, and with boiling points between 50 and 70 °C. Hexanes are used in the formulation of glue for shoes, leather products, and roofing. There are 5 isomers of hexane including n-hexane, 2- and 3-methylpentane, 2,2- and 2,3-dimethylbutane (Table 4).

Table 4. Isomers of Hexane and CAS No.

Isomer Name	CAS No.	Chemical Structure
n-hexane	110-54-3	
2-methylpentane	107-83-5	
3-methylpentane	96-14-0	
2,3-dimethylbutane	79-29-8	
2,2-dimethylbutane	75-83-2	

n-Hexane (hexane) is a solvent that has many uses in the chemical and food industries, either in pure form or as a component of the commercial hexane mixture. Highly purified hexane is primarily used as a reagent for chemical or chromatographic separations. Commercial hexane is a mixture that contains approximately 52% hexane; the remaining balance is made up of varying amounts of structural isomers and related chemicals, such as methylpentane and methylcyclopentane. Mixtures containing hexane are also used in the extraction of edible fats and oils in the food industry, as cleaning agents in textile and furniture manufacturing, and in the printing industry. Hexane is the solvent base for many commercial products, such as glues, cements, paint thinners, and degreasers. The chemical is a minor constituent of crude oil and

natural gas and, therefore, represents a variable proportion of different petroleum distillates. For example, hexane comprises about 11.6% of unleaded gasoline and about 2% of JP-4 aviation fuel (ATSDR, 1993b, 1999, USEPA 2005).

The most probable route of human exposure to hexane is by inhalation. Individuals are most likely to be exposed to hexane in the workplace; however, monitoring data indicate that hexane is a widely occurring atmospheric pollutant. Exposure from contact with vapors or emissions from heating and motor fuels refined from petroleum products is the most widespread form of low-level exposure for the general population. Most hexane in these fuels is oxidized, or destroyed, as part of the combustion process to provide heat or drive internal combustion engines. Small amounts of hexane, along with other petroleum compounds, volatilize to the atmosphere during handling, storage in fuel tanks, or through incomplete combustion. Recent research suggests that certain fungi may be able to produce hexane. These fungi may be common in older buildings, and in some parts of the country may provide exposures from previously unsuspected indoor sources (ATSDR 1993a, 1999, NSC 2003).

In Texas, the highest reported 1-hour (h) concentration (from 1996 through 2016) of n-hexane was 380.2 ppb collected from an automated gas chromatograph (AutoGC) sample at an ambient air monitoring site at the Decatur Thompson monitoring site in Dallas in 2013. The highest represented annual concentration of n-hexane was 1.4 ppb measured at the Clinton monitoring site in Houston in 1998. The highest 24-h n-hexane value collected from a canister sample from 1995 to 2015 was 690.7 ppb at the Beaumont Downtown monitor in 1996. The highest represented annual concentration of n-hexane was 13.4 ppb measured at the Beaumont Downtown in 1996.

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

The main chemical and physical properties of n-hexane are summarized in Table 3. Chemical and physical properties for other hexane isomers are similar to n-hexane.

3.2 Health-Based Acute ReV and ESL

Inhalation of n-hexane usually causes eye, nose, throat and respiratory irritation, which are rapidly reversible when exposure is discontinued. Acute effects are considered similar to that of other saturated aliphatic hydrocarbons of similar length (C_3-C_8 alkanes) (EU 2003). However, there is a direct relationship between aliphatic carbon chain length and the potency of alkanes for effects such as lethality, anesthetic activity, physiological response, respiratory irritation, and neurological toxicity (i.e., as chain length increases up to C_{10}, toxicity increases) (Patty and Yant 1929, Glowa 1991, Swann et al. 1974, Lammers et al. 2011). One reason is, as carbon chain

length of alkanes increases and the potency increases, the higher number of carbon atoms in aliphatic hydrocarbons have higher uptake rates (Dahl et al. 1988, McKee et al. 2006, Lammers et al. 2011). Furthermore, elimination of low-molecular-weight hydrocarbons is predominantly by exhalation and very rapid whereas elimination of molecules of greater molecular weights is more likely to involve metabolism and urinary excretion, increasing elimination half times from a few minutes (min) to approximately 2 h (Lammers et al. 2011). Studies of the comparative inhalation toxicities of the saturated hydrocarbons showed that straight-chain alkanes are more toxic than their branched isomers (Lazarew 1929, as cited in Carreón T. 2005).

3.2.1 Key Animal Study (Glowa 1991)

Glowa (1991) examined the ability of individual n-alkanes (C_5-C_8) including n-hexane 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 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-min of exposure of incrementally increased hexane 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 less than 3,000 ppm had no effect. Concentrations of 5,600 ppm n-hexane decreased the rate of response in a concentration-related manner with decreased rate of response of slightly less than 50% at 5,600 ppm, about 80% at 8,000 ppm, and completely abolishing it (100%) at 17,000 ppm. Response recovered fully 30 min following ceasing exposure to 17,000 ppm n-hexane. Mean concentrations (± standard deviation) resulting in a 50% and 10% rate of response-decreasing potency (EC_{50} and EC_{10}) were 7,051 ± 3,138 and 4,537 ± 3,490 ppm, respectively. The level of 3,000 and 4,537 ppm (EC_{10}) can be considered a 30-min no-observed-adverse-effect-level (NOAEL) and minimal lowest-observed-adverse-effect-level (NOAEL), 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 n-hexane (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 1,000 ppm compared to the control. ACTH levels increased sharply approximately 1,400% and 1,700% of control at 3,000 and 10,000 ppm, respectively. The levels of 1,000 and 3,000 ppm may be considered a 30-min NOAEL and LOAEL, respectively, for HPA

activation. However, no statistical analyses were performed and thus, statistical significance is unknown. Without knowing the biological significance of the neuroendocrine effects as measured by HPA activation, or the statistical significance of the effects, we could not determine if the effects were adverse. Nevertheless, the 30-min NOAEL of 1,000 ppm for neuroendocrine effects was conservatively used as point of departure (POD) to develop the 1-h acute ReV for n-hexane.

3.2.2 Supporting Studies

3.2.2.1 Swann et al. (1974) Animal Study

Swann et al. (1974) studied the respiratory tract irritation properties of n-hexane in male Swiss mice (25 g). Four animals were exposed head-only for 5 min at each of the following concentrations of n-hexane: 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, and 64,000 ppm (nominal concentrations). The respiratory rate, depth, and configuration were counted and recorded for 15-second intervals while the animals were inhaling n-hexane. Concentrations up to 8,000 ppm produced no anesthesia. At 16,000 ppm, mice experienced some periodic body movement during exposure. Some slight anesthesia occurred during the recovery period. At 32,000 ppm, mice experienced respiratory irregularity during exposure with deeper anesthesia and increased expiratory effect. At 64,000 ppm, all mice stopped breathing within 4.5 min of the onset of exposure. A NOAEL and LOAEL of 8,000 and 16,000 ppm, respectively, for irritation were identified from this study. Since the exposure duration was only 5 min, the NOAEL was not used as a POD to develop the acute toxicity values.

3.2.2.2 Patty and Yant (1929) Human Study

In a human inhalation study, no symptoms were experienced by three to six volunteers exposed to 2,000 ppm hexane for 10 min, but dizziness and a sense of giddiness were experienced at 5,000 ppm (Patty and Yant 1929). This study is rather dated and focused on a limited number of parameters to examine the warning properties of C_3-C_7 alkanes, evaluated only 3-6 subjects, study results were not well reported, and exposure was for only 10 min. Thus, the NOAEL of 2,000 ppm identified from this study was not used as the POD to derive the acute ReV and ^{acute}ESL for n-hexane.

3.2.2.3 Rebert and Sorenson (1983, as cited in ATSDR 1999) Animal Study

In a subacute study by Rebert and Sorenson (1983, as cited in ATSDR 1999), the body weights of male Fischer 344 rats exposed to 1,500 ppm n-hexane 24 h/day (d), 5 d/week (wk) were 11% below those of control rats within 2 wk. Statistical significance was not reported. The level of 1,500 ppm can be considered a free-standing LOAEL for decrease in body weight gain. Since the study was for subacute exposure (24 h/d), even if a 1-h LOAEL adjusted from a single 24-h exposure were deemed appropriate in this case (the duration of actual exposure was > 100 h),

the LOAEL from this subacute study would be much higher so was not used as POD to develop the acute ReV.

3.2.2.4 Other Animal Studies

In another study, a NOAEL of 500 ppm was reported after a 5-min inhalation exposure in an unidentified test species (Wayne and Orcutt 1960). Iba and Bird (2007) reported that rats exposed to 1,000 ppm for 6 h experienced no adverse health effects when compared to other treatment groups. This study did not clearly identify a NOAEL for hexane exposure as the purpose of the study was to examine the effects of co-exposure of rats to hexane and the 1,3-butadiene metabolite, 3-butene-1,2-diol. However, the findings of the Iba and Bird (2007) study add further evidence to the relatively nontoxic nature of hexane. The NOAEL is likely to be at least 1,000 ppm for exposure to hexane alone.

3.2.3 Reproductive/Developmental Toxicity Studies

No information is available on the reproductive or developmental effects of hexane in humans. Several animal reproductive/developmental animal studies are available but the results (both NOAELs and LOAELs) vary considerably. Most studies (Mast et al. 1988, Litton Bionetics 1979, Bus et al.1979, Neeper-Bradley (1989a,b)), however, do not indicate that n-hexane exposure produces adverse reproductive/developmental effects. While the USEPA indicates that the results of the Mast et al. (1987) rat study were questionable, the level of 1,000 ppm was conservatively considered a minimal LOAEL for reduction in fetal body weight identified in this study.

3.2.3.1 Mast el at. (1987) Animal Study

In an animal study, pregnant Sprague-Dawley (SD) rats (30/group) were exposed to 0, 200, 1,000, or 5,000 ppm n-hexane by inhalation for 20 h/d over gestation (GD) 6-19 for rats (Mast et al. 1987, as cited in NTP 1991 and ATSDR 1999). Maternal toxicity (reduced maternal extra-gestational weight gain) was statistically significant only for the 5,000 ppm exposure group. A NOAEL and LOAEL of 1,000 and 5,000 ppm, respectively, for maternal toxicity was identified. No major abnormalities were seen in any of the fetuses. A statistically significant increased incidence of reduced skeletal ossification of sternebrae 1-4 was observed at 5,000 ppm, and the increase was positively correlated with increasing exposure concentration. No significant differences were observed in intrauterine death rate, or in the incidence of fetal malformations. A statistically significant reduction in fetal body weight relative to controls was observed for males at the 1,000 and 5,000 ppm exposure levels (7 and 15% reduction, respectively). Female fetal body weights were also reduced with respect to controls at the 1,000 and 5,000 ppm exposure levels (3 and 14% reduction, respectively), but the reduction was only statistically significant for the 5,000 ppm group. A NOAEL and LOAEL of 200 and 1,000 ppm for decreases in fetal body weights were identified from this study.

USEPA (2005), however, indicated that the range between the NOAEL and LOAEL is considerable. Further, the USEPA indicates that several additional studies (Mast et al. 1988, Litton Bionetics 1979, Bus et al.1979, Neeper-Bradley 1989a,b) do not indicate that n-hexane exposure produces adverse reproductive/developmental effects. The USEPA indicated that the NOAEL and LOAEL for decreased fetal body weights identified from the Mast et al. (1987) study are questionable. Nevertheless, according to the TCEQ Guidelines (2015a), the statistically significant reduction in fetal body weight (7%) relative to controls observed for males at 1,000 ppm was considered minimal adverse effect as the reduction in fetal body weight was > 5%. Since the minimal LOAEL of 1,000 ppm was conducted for 20 h/d and based on a developmental effect, it was not used to derive 1-h acute ReV. However, it was used as POD to derive the 24-h ReV for the evaluation of ambient air monitoring data (Section 3.3).

3.2.3.2 Mast et al. (1988) Animal Study

Groups of 35 pregnant Swiss mice were exposed to n-hexane for 20 h/d during GD 6-17 at 0, 200, 1,000, and 5,000 ppm (Mast et al .1988, as cited in ATSDR 1999). Maternal body weight was significantly reduced (6%) at 5,000 ppm, and this was accompanied by a decrease in mean gravid uterine weight. There was no effect on body weight in a group of 10 non-pregnant mice co-exposed to n-hexane at 5,000 ppm in this experiment. The mean ratio of uterine weight to extra-gestational weight gain for all treatment groups was less than for the controls and this difference was statistically significant for the 5,000 ppm group. The number of live fetuses per litter was significantly reduced at 5,000 ppm, with a significant concentration-dependent trend. The number of resorptions per litter was significantly increased at 200 ppm, but not at higher concentrations. Fetal weights (male and female combined) were slightly, but not significantly, reduced for all treatment groups compared to controls. However, the decrease was significantly correlated to increasing n-hexane concentration. Male fetal weights for n-hexane exposure groups were not significantly affected compared to controls, but female fetal weights were significantly reduced for the 5,000 ppm group compared to controls. There was no increased incidence of malformations or variations in any group exposed to n-hexane. The level of 1,000 and 5,000 ppm can be considered the reproductive/developmental NOAEL and LOAEL, respectively (e.g., number of live fetuses per litter, decreased female fetal body weight).

3.2.3.3 Litton Bionetics (1979) Animal Study

In a developmental study where pregnant SD rats were exposed to n-hexane concentrations of 0, 93, and 409 ppm for 6 h/d over GD 6-15, no effects on body weight of the dams were observed (Litton Bionetics 1979, as cited in ATSDR 1999). No effects on body weight of the dams and no statistically significant difference in skeletal abnormalities between control and treated groups were observed. All animals were normal in appearance throughout the study. The level of 409 ppm was a free-standing NOAEL for developmental effects.

3.2.3.4 Bus et al. (1979) Animal Study

Pregnant Fischer 344 rats (7/group) were exposed to 0 or 1,000 ppm n-hexane for 6 h/d during GD 8-12, 12-16, or 8-16 (Bus et al.1979). No significant alterations in fetal resorptions, body weights, visible anomalies, or the incidence of soft tissue and skeletal anomalies were noted in any of the treatment groups. A temporary decrease in pup weight gain was seen in the offspring from dams exposed during GD 8-16. A low, nonsignificant incidence of misaligned fourth sternebrae was noted in each of the treatment groups. The level of 1,000 was a free-standing NOAEL.

3.2.3.5 Neeper-Bradley (1989a,b) Animal Studies

In a study by Neeper-Bradley (1989a,b as cited in ATSDR 1999), groups of pregnant SD rats (n=25/group) and CD-1 mice (30/group) were exposed to commercial hexane (contains 53.4% n-hexane, unspecified hydrocarbons for the remaining) vapor at 0, 914, 3,026, and 9,017 ppm for 6 h/d on GD 6-15. No significant differences between groups were observed in rats for the number of viable implantations per litter, number of nonviable implantations per litter, sex ratio, fetal body weights (total, male and female), incidence of variations by category, incidence of individual or pooled external, visceral or skeletal malformations or total malformations, or of total variations. Maternal toxicity (reduced weight gain) was observed in rats at 3,026 and 9,017 ppm, but total weight gain throughout pregnancy was unaffected by exposure. The authors concluded that exposure to commercial hexane vapor by inhalation during organogenesis in SD rats resulted in maternal toxicity at 3,026 and 9,017 ppm, with no apparent developmental toxicity at any level.

In mice, a significantly increased incidence of poor ossification was observed at 2 of the 84 sites examined (bilateral bone island at the first lumbar arch and all intermediate phalanges of the hindlimb unossified) in the 9,017 ppm group. Slight maternal toxicity (color changes in the lungs at necropsy) was also observed in mice at 3,026 and 9,017 ppm. The authors concluded that exposure to commercial hexane vapor by inhalation during organogenesis in the CD-1 mouse resulted in slight maternal toxicity at 3,026 and 9,017 ppm and slight developmental toxicity (poor ossification in the absence of malformations) at 9,017 ppm. A NOAEL and LOAEL of 914 and 3,026 ppm, respectively, for maternal toxicity and a NOAEL and LOAEL of 3,026 and 9,017 ppm, respectively, for developmental effects were identified from this study.

3.2.3.6 Daughtrey et al. (1992, 1994) Two-Generation Reproductive Study

In a two-generation reproductive study (Daughtrey et al. 1992), male and female SD rats (25/sex/group) were exposed to commercial hexane (contains 53% n-hexane, 16% 3-methyl pentane, 14% methylcyclopentane, and 12% 2-methyl pentane) vapor at target concentrations of 0, 900, 3,000, or 9,000 ppm for 6 h/d, 5 d/wk, over two generations. At both the F0 breed to produce F1 litters and the F1 breed to produce F2 litters, reproductive parameters were

unaffected. Litter size and postnatal survival were not significantly different between exposure groups. However, reductions in body weight and body weight gain were observed in both F1 and F2 litters exposed to 9,000 ppm. Effects on body weight were not observed in offspring exposed to the 900 or 3,000 ppm. Histopathologic examination of selected organs revealed hyaline droplet nephropathy in adult F0 and F1 males exposed to 9,000 ppm. No other treatment related lesions were observed. A NOAEL and LOAEL of 3,000 and 9,000 ppm for reduction in body weight and body weight gain, and a free-standing NOAEL of 9,000 ppm for reproductive effects were identified from this study.

3.2.3.7 Summary of Reproductive/Developmental Studies

The results of these animal reproductive/developmental studies are summarized in Table 5.

Table 5 Summary of Reproductive/Developmental Animal Inhalation Studies

Study	Animal Strain	Exposure Duration	Exposure Concentration	NOAEL	LOAEL[a]	Response at LOAEL
Mast et al. (1987)	Pregnant SD rats (30/group)	20 h/d over GD 6-19	0, 200, 1,000, or 5,000 ppm	1,000 ppm	5,000 ppm	Maternal toxicity (reduced in extra-gestational maternal weight gain in dams)
				200 ppm	1,000 ppm[b] (minimal)	Reduced in fetal body weight (7%) in males
				1,000 ppm	5,000 ppm	Reduced in fetal body weight (14%) in females
Mast et al. (1988)	Pregnant Swiss mice	20 h/d over GD 6-17	0, 200, 1,000, or 5,000 ppm	1,000 ppm	5,000 ppm	Reduced in number of live fetuses per litter; and fetal body weight in females
				5,000 ppm	---	Absence of reduced in fetal body weight in males
Litton Bionetics (1979)	Pregnant SD rats (155-188/group)	6 h/d over GD 6-15	0, 93, and 409 ppm	409 ppm	---	Absence of maternal toxicity and developmental effect
Bus et al. (1979)	Fischer 344 rats (7/group)	6 h/d over GD 8-12, 12-16, or 8-16	0, or 1,000 ppm	1,000 ppm	---	Absence of maternal toxicity and developmental effect

Study	Animal Strain	Exposure Duration	Exposure Concentration	NOAEL	LOAEL[a]	Response at LOAEL
Neeper-Bradley (1989a)	Pregnant SD rats (25/group)	6 h/d on GD 6-15	0, 914, 3,026, and 9,017 ppm of commercial hexane	914 ppm	3,026 ppm	Slight maternal toxicity (reduced weight gain in dams) in mice
				9,017 ppm	---	Absence of developmental effect
Neeper-Bradley (1989b)	Pregnant CD-1 mice (30/group)	6 h/d on GD 6-15	0, 914, 3,026, and 9,017 ppm	914 ppm	3,026 ppm	Slight maternal toxicity (color changes in the lungs at necropsy)
				3,026 ppm	9,017 ppm	Slight developmental effect (increased incidence of poor ossification)
Daughtrey et al. (1992, 1994)	SD male and female rats (25/sex/group)	6 h/d, 5 d/wk, over two generations	0, 900, 3,000, and 9,000 ppm (target concentrations)	9,000 ppm	---	No effects on reproduction
				3,000 ppm	9,000 ppm	Reductions in body weight and body weight gain were observed in both F1 and F2 litters; and hyaline droplet nephropathy in adult F0 and F1 males

[a] P< 0.05
[b] Minimal LOAEL for developmental effect and used as POD.to derive 24-h ReV

In summary, the results of reproductive/developmental studies in animals are inconsistent. The NOAELs and LOAELs for developmental effects range from 200 to 9,017 and 1,000 to 9,017 ppm, respectively. As described in Section 3.2.3.1, the minimal LOAEL of 1,000 ppm for reduction in fetal body weight due to 20 h/d exposure over GD 6-19 was used as the POD to derive a 20-h ReV for developmental effects. The derived 20-h ReV can be used as a 24-h ReV for the evaluation of 24-h ambient air monitoring data (See Section 3.3)

The NOAELs and LOAELs for maternal toxicity from these studies range from 409 to 1,000 and 3,036 to 5,000 ppm, respectively.

3.2.4 Mode of Action (MOA) Analysis and Dose Metric

n-Hexane is metabolized in vivo to hydroxyl derivatives (2-hexanol, 2-hexanone, 2,5-hexanediol, 2-hydroxy-5-hexanone, and 2,5-hexanedione) via a cytochrome p450 oxidase system. 2,5-Hexanedione is believed to be the major toxic metabolite produced in humans (USEPA 2005).

The 1- and 3-hexanol formed are conjugated with glucuronic acid or undergo further oxidation to hexanoic acid.

The MOA for neurotoxic effects is attributed to n-hexane's neurotoxic metabolite, 2,5-hexanedione. The MOA for developmental/reproductive effects are also related to 2,5-hexadione (Isobe et al. 1998, Cheng et al. 2012). Data on the exposure concentration of the parent chemical are available, whereas data on more specific dose metrics are not available. Thus, exposure concentration to the parent chemical will be used as the dose metric.

3.2.5 POD and Critical Effect

For n-hexane, 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 1-h acute ReV. The critical effect was transient neuroendocrine effects.

3.2.6 Dosimetric Adjustments

3.2.6.1 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).

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

3.2.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

n-Hexane is practically water insoluble. Acute exposures to hexane cause transient behavioral impairment and neurological function impairment, respectively, which are systemic effects. In addition, toxicokinetic data indicate that n-hexane is rapidly absorbed via the lungs and widely distributed within the body. n-Hexane 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-hexane are 0.8 and 1.72, 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). Because the ratio of the animal-to-human partition coefficients (1.72/0.8 = 2.15) is greater than one, a default value of one is used as the regional gas dose ratio as recommended by TCEQ (2015a). The resulting POD_{HEC} from the POD_{ADJ} of 500 ppm is 500 ppm for n-hexane.

3.2.7 Adjustments of the POD_{HEC}

The POD_{HEC} of 1,000 ppm for neuroendocrine effects was used to derive the 1-hour acute ReV and ^{acute}ESL for n-hexane. The following uncertainty factors (UFs) were applied to the POD_{HEC}: a UF of 10 for human variability (UF_H), a UF of 3 to account for interspecies variability (UF_A), and a UF of 3 to account for database uncertainty (UF_D) for a total UF = 90:

- UF_H of 10 for intraspecies variability,
- 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,
- UF_D of 3 was used for uncertainty associated with an incomplete database. A higher UF_D was not used because one human study was reported and several animal studies were conducted for different toxicity endpoints including 2-generation reproductive/developmental effects, and multiple animal species were used in inhalation bioassays. Consistent with TCEQ (2015a), confidence in the database is considered medium-high. The quality of the key rat study is medium to high.

$$\text{Acute ReV [1-h]} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$

$$= 500 \text{ ppm} / (10 \times 3 \times 3)$$
$$= 5.5555 \text{ ppm}$$
$$= 5{,}500 \text{ ppb (rounded to two significant figures)}$$

3.2.8 Health-Based 1-h Acute ReV and ^{acute}ESL

In deriving the 1-h 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 1,600 ppb (5,600 µg/m^3) for n-hexane is based on the acute ReV of 5,500 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 6).

Table 6. Summary of 1-h Acute ReV and ^{acute}ESL for n-Hexane

Parameter	Values and Descriptions
Study	Glowa (1991)
Study Quality	High
Study Population	Adult male CD-1 mice (4-6 mice/group)
Exposure Method	Incrementally increasing exposure inhalation from 100 ppm up to 10,000 ppm
Exposure Duration	30-min
Critical Effects	Neuroendocrine effects
POD (NOAEL)	1,000 ppm
POD_{ADJ} to 1h	500 ppm
POD_{HEC}	500 ppm
Total UFs	90
Intraspecies UF	10
Interspecies UF	3
Extrapolation from LOAEL to NOAEL	Not available
Incomplete Database UF *Database Confidence*	3 Medium
Acute ReV [1 h] (HQ = 1)	**5,500 ppb (19,000 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**1,600 ppb (5,600 µg/m^3)**

3.3 Health-Based Acute 24-Hour ReV

The minimal LOAEL of 1,000 ppm for decreased fetal body weight from the Mast et al. (1987) study was used as POD to derive the acute 24-h ReV (Section 3.2.3.1 and 3.2.3.7).

3.3.1 Dosimetric Adjustments

3.3.1.1 Exposure Duration Adjustments

The POD of 1,000 ppm was based on developmental effects conducted for 20 h/d during GD 6-19. No exposure duration adjustment was conducted, i.e., from a 20-h to a 24-h, for reproductive/developmental studies (TCEQ 2015a). Thus, the 20 h of the single day of exposure was used for 24-h ReV. The POD_{ADJ} resulting from the POD of 1,000 ppm is 1,000 ppm.

3.3.1.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

As described in Section 3.2.6.2, because the ratio of the animal-to-human partition coefficients (1.72/0.8 = 2.15) is greater than one, a default value of one is used as the RGDR. The resulting 24-h POD_{HEC} from the 24-h POD_{ADJ} of 1,000 ppm is 1,000 ppm for n-hexane.

3.3.2 Adjustments of the POD_{HEC}

The POD_{HEC} of 1,000 ppm for developmental effect was used to derive the 24-hour acute ReV and ^{acute}ESL for n-hexane. The following UFs were applied to the POD_{HEC} (Total UF = 180):

- UF_H of 10 for intraspecies variability,
- 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,
- UF_L of 2 for extrapolation from a minimal LOAEL to NOAEL. A higher UF_L was not used because the reduction in fetal body weight (7%) was in males only and only marginally above 5%, and NOAELs identified from other similar studies for developmental endpoint are at or greater than the minimal LOAEL of 1,000 ppm (Table 5), and
- UF_D of 3 was used for uncertainty associated with an incomplete database. A higher UF_D was not used because several animal reproductive/developmental studies including 2-generation reproductive/developmental effects were conducted for different toxicity endpoints, and multiple animal species were used in inhalation bioassays. Consistent with TCEQ (2015a), confidence in the database is considered medium-high. The quality of the key rat study is medium to high.

$$\text{Acute ReV [24-h]} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$

$$= 1{,}000 \text{ ppm} / (10 \times 3 \times 2 \times 3)$$
$$= 5.5555 \text{ ppm}$$
$$= 5{,}500 \text{ ppb } (19{,}000 \ \mu g/m^3) \text{ (rounded to two significant figures)}$$

3.3.3 Health-Based 24-h Acute ReV

In deriving the 24-h 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 24-h acute ReV is 5,500 ppb (19,000 $\mu g/m^3$) (Table 7).

Table 7. Summary of 24-h Acute ReV

Parameter	Values and Descriptions
Study	Mast et al. 1987
Study Quality	Medium to high
Study Population	pregnant Sprague-Dawley (SD) rats (30/group)
Exposure Method	0, 200, 1,000, or 5,000 ppm n-hexane by inhalation
Exposure Duration	20 h/d over gestation (GD) 6-19 for rats
Critical Effects	decreased fetal body weights
POD	1,000 ppm (minimal LOAEL)
POD_{ADJ} to 24h	1,000 ppm
POD_{HEC}	1,000 ppm
Total UFs	180
Intraspecies UF	10
Interspecies UF	3
Extrapolation from LOAEL to NOAEL	2
Incomplete Database UF *Database Confidence*	3 High
Acute ReV [24 h] (HQ = 1)	**5,500 ppb (19,000 µg/m^3)**

3.4 Welfare-Based Acute ESLs

3.4.1 Odor Perception

Hexane is a colorless liquid that has an associated gasoline-like odor. A 50% odor detection threshold value of 5,300 µg/m^3 (1,500 ppb) was reported for hexane by Nagata (2003) utilizing the triangular odor bag method. Since hexane does not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015b).

3.4.2 Vegetation Effects

Haagen-Smit et al (1952) conducted a screening study on the effects of hexane on spinach (*Spinacia oleracea*), endive (*Cichorium endivia*), beets (*Beta vulgaris*), oats (*Avena sativa*), and alfalfa (*Medicago sativa*). Fumigations in this study were conducted in a small glass chamber

with a 353 L capacity at concentrations of 25 ppm or greater for minimum exposure duration of 5 h. No damage was observed as a result of exposure to hexane at 25 ppm, which was designated as a NOAEL. According to the ESL guidelines (TCEQ 2015a), TCEQ determined an acute-vegetation ESL of 25 ppm as a threshold concentration from the study. However, as the reported vegetative effects were significantly above other health- and odor-based concentrations and the study was of insufficient quality, an $^{acute}ESL_{veg}$ was not developed for hexane.

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

3.5.1 n-Hexane

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

- Acute ReV [1-h] = 19,000 µg/m^3 (5,500 ppb)
- Acute ReV [24-h] = 19,000 µg/m^3 (5,500 ppb)
- ^{acute}ESL = 5,600 µg/m^3 (1,600 ppb)

For the evaluation of ambient air monitoring data, the level of 5,500 ppb (19,000 µg/m^3) are used for both 1-h and 24-h ReV (Table 1). The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 5,600 µg/m^3 (1,600 ppb) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5.2 Other hexane Isomers

No acute toxicity data were available describing the potential acute toxicity of other hexane isomers. For the purpose of health effects evaluations for ambient air monitoring data, the acute 1-h and 24-h ReV value of 19,000 µg/m^3 (5,500 ppb) for n-hexane will be used as surrogates. For the purpose of health effects evaluations for air permit applications, the ^{acute}ESL of 5,600 µg/m^3 (1,600 ppb), as n-hexane, will be used.

3.6 Acute Inhalation Observed Adverse Effect Levels (IOAELs)

The acute inhalation observed adverse effect level (^{acute}IOAEL) of 1,000 ppm for n-hexane was based on the 20-h $LOAEL_{HEC}$ of 1,000 ppm for developmental effects from the rat study (Mast et al. 1987). No duration adjustments were made although default animal-to-human dosimetric adjustments were performed. Effects occurred in some animals and the ^{acute}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 ^{acute}IOAEL level is provided for informational purposes only (TCEQ 2015a). The ^{acute}IOAEL for n-hexane is:

- n-Hexane ^{acute}IOAEL = 3,500 mg/m^3 (1,000 ppm) (rounded to 2 significant figures)

The margin of exposure between the ^{acute}IOAEL (1,000 ppm) and the acute ReV (5.5 ppm) for n-hexane is a factor of ~180.

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

There is not sufficient data to link exposure of hexane to a carcinogenic endpoint. In addition, inconclusive data exists regarding the exact nature of the dose-response relationship associated with hexane and its toxic endpoints in regards to the dose-response relationship. Therefore, hexane is classified as a noncarcinogen and the default threshold (nonlinear) approach was used.

4.2.1 Key Studies

Based on reports from both human and animal studies, the most sensitive toxic endpoint resulting from n-hexane exposure is peripheral neuropathy, which is a condition characterized by loss of sensation and muscular control (Yamada S. 1967, Yamamura Y. 1969, Schaumberg and Spencer 1976, Seppalainen et al. 1979, Sanagi et al. 1980, Dunnick et al. 1989, Huang et al. 1989, Daughtrey et al. 1999). The human occupational inhalation study by Chang et al. (1993) and the rodent inhalation study by Miyagaki (1967) were selected as the key studies. Both studies were well-conducted and hexane-induced peripheral neuropathy was the toxic-endpoint of interest in each study. Both were chosen as the key chronic studies.

4.2.1.1 Chang et al (1993) Human Study

In the Chang et al (1993) study, symptomatic peripheral neuropathy was reported in 20 of 56 workers (36% of workers) in an offset printing factory and another 26 workers (approximately 46%) were asymptomatic but had evidence of subclinical neuropathy. Other reported effects included reductions in both sensory and action potentials, decreases in motor nerve conduction velocity and increased distal latency. In one severe case, a sural nerve biopsy revealed giant axonal swellings with accumulation of 10 nm neurofilaments, myelin sheath attenuation, and widening of nodal gaps. Optic neuropathy and CNS impairment were not common among the 56 workers evaluated in this study. Personal air samples were used to determine a range of exposure concentrations of 80 to 210 ppm (mean = 132 ppm) hexane, and 20-680 ppm (mean = 235 ppm) isopropanol and 20-84 ppm (mean = 50 ppm) toluene. At this particular factory, the

workers worked 12 h/d, 6 d/wk, and the mean duration of employment was 2.6 years, with a range of 1 month to 30 years. The range of employment duration provided sufficient exposure durations to classify the Chang et al. (1993) study as a chronic study. The mean hexane exposure concentration of 132 ppm determined in this study was designated as a lowest-observed-adverse-effect-level (LOAEL). The LOAEL was used as the POD to derive chronic ReV and ESL.

4.2.1.2 Miyagaki (1967) Animal Study

In the Miyagaki (1967) study, 6 groups of 10 male SM-A mice, a transgenic strain of mice , were housed in a gas-chamber and were exposed to 0, 100, 250, 500, 1,000, or 2,000 ppm commercial grade hexane (65-70% n-hexane and 30-35% other hexane isomers) for 24 h/d, 6 d/wk for one year. It was determined that animals exposed to 250 ppm of hexane or higher for one year exhibited symptoms of peripheral neuropathy, such as abnormal posture, muscular atrophy, and various endpoints resulting from electrophysiological tests assessed nerve conductivity and muscle responses in mice. Based on the findings of this study by Miyagaki (1967), the 100 ppm treatment group showed no signs of physical impairment; therefore, this was designated as the NOAEL for this study. The level of 250 ppm was designated as the LOAEL. The NOAEL was also used as the POD to derive chronic ReV and ESL.

4.2.2 Supporting Studies

There are quite a few chronic inhalation studies of n-hexane conducted in both humans and animals (USEPA 2005). Some relevant studies cited by USEPA (2005) are summarized below (Table 8).

Table 8. Summary of Supporting Subchronic/Chronic Inhalation Studies of n-Hexane

Study	Species	Exposure Duration	Exposure Concentration	NOAEL	LOAEL	Response at LOAEL
Sanagi et al. (1980)	Male workers (14/ group)	8 h/d, 5 d/wk, for 1-12 years (average of 6.2 years)	Control, or 58 ppm for n-hexane and 39 ppm for acetone (8-h TWA)	58 ppm	---	Absence of peripheral neuropathy
				---	58 ppm	Statistically significant increased incidence of subject-reported symptoms, neurological tests, and neuro-physiological findings
Dunnick et al. (1989)	B6C3F1 mice (10/sex/ group)	6 h/d, 5 d/wk for 13 wk	0, 500, 1,000, 4,000, or 10,000 ppm	4,000 ppm	10,000 ppm	Reduction in locomotor activity in females. Increased incidence of paranodal axonal swelling
		22 h/d, 5 d/wk for 13 wk	1,000 ppm	---	1,000 ppm	Reduction in locomotor activity. Increased incidence of paranodal axonal swelling
Ono et al. (1982)	Male Wistar rats (8/group)	12 h/d, 7 d/wk for 24 wk	0, 200, or 500 ppm	---	200 ppm	Statistically significant decreased in motor nerve conduction velocity (MCV), and degeneration of the myelinated axons
Huang et al. (1989)	Male Wistar rats (8/group)	6 h/d, 5 d/wk for 13 wk	0, 500, 1,200, or 3,000 ppm	500 ppm	1,200 ppm	Statistically significant reduction in body weight gain, reduction in MCV. Neurophysiologic deficits and histopathologic effects were observed
Daughtrey et al. (1999)	F344 rats and B6C3F1 (50/sex/ group)	6 h/d, 5 d/wk for 2 years	0, 900, 3,000, or 9,000 ppm commercial hexane	---	900 ppm	Histopathological lesions of the respiratory tract and squamous metaplasia or hyperplasia of the columnar epithelium. Statistically significant increase incidence of pituitary adenomas in exposed female mice
				3,000 ppm	9,000 ppm	Statistically significant increase in the incidence of hepatocellular neoplasms in the liver of exposed female mice

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

The metabolism of hexane is described in Section 3.2.4. The MOA for neurotoxic effects is attributed to n-hexane's neurotoxic metabolite, 2,5-hexanedione.

Data on exposure concentration of the parent chemical is available in both the Chang et al. (1993) study and the Miyagaki (1967) study, whereas data on more specific dose metrics are not available. Thus, exposure concentration of the parent chemical will be used as the default dose metric.

4.2.4 Critical Effect and POD

In order to determine the critical effect amongst multiple endpoint PODs, POD_{HECs} for the LOAELs from both the Chang et al. (1993) human study and the Miyagaki (1967) mouse study were determined. The lower LOAEL-based POD_{HEC} determines the critical effect for derivation of the chronic ReV and ESL (TCEQ 2015a). The chronic LOAEL is 132 ppm for the Chang et al. (1993) study and 250 ppm for the Miyagaki (1967) study. After dosimetric adjustments, the POD_{HECs} for the LOAELs from the Chang et al. (1993) and Miyagaki (1967) studies were 57 and 250 ppm, respectively. Therefore, peripheral neuropathy is the chronic critical effect and the LOAEL of 132 ppm identified from the Chang et al. (1993) key study was used as the POD to derive chronic ReV and $^{chronic}ESL_{threshold(nc)}$. The details of determination of the POD_{HECs} for the LOAELs are described in Appendix A.

4.2.5 Dosimetric Adjustments

4.2.5.1 Exposure Duration Adjustments

The occupational POD (PODoc) from the Chang et al. (1993) study was adjusted to a POD that is representative of a human equivalent concentration applicable to the general population (POD_{ADJ}) according to section of 4.2.1 of the ESL guidelines (TCEQ 2006) by using the following dosimetric adjustment formula:

$$POD_{ADJ} = POD_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/d)

VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/d)

$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)

$\text{days per week}_{res}$ = residential weekly exposure frequency (7 d/ week)

In the formula listed above, the default occupational ventilation rate of 10 m^3/d was determined for an 8-h workday and the workers in the Chang et al. (1993) study worked 12 h/d.

However, based on scientific judgment, use of the default ventilation rate based on an 8-h workday was considered conservative for use in the derivation of POD_{HEC}.

$$POD_{ADJ} = 132 \text{ ppm} \times (10/20) \times (6/7) = 57 \text{ ppm}$$

4.2.6 Adjustments of the POD_{HEC}

The POD_{HEC} of 57 ppm for peripheral neuropathy was used to derive the chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for n-hexane. The following UFs were applied to the POD_{HEC} (Total UF = 300):

- a UF_H of 10 for intraspecies variability,
- a UF_L of 10 for extrapolation from a free-standing LOAEL to NOAEL, and
- a UF_D of 3 was used for uncertainty associated with an incomplete database. There are multiple human and animal studies and several animal studies were conducted for different toxicity endpoints including 2-generation reproductive/developmental effects, and multiple animal species were used in inhalation bioassays. As described by USEPA (2005), a lower UFD of 1 was not used because the lack of multigeneration reproductive and developmental studies following exposure to pure n-hexane and the uncertainty associated with low-dose developmental effects of exposure to n-hexane. Consistent with TCEQ (2015a), confidence in the database is considered medium to high. The quality of the key human study is high.

$$\text{Chronic ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$

$$= 57 \text{ ppm} / (10 \times 10 \times 3)$$
$$= 0.19 \text{ ppm}$$
$$= 190 \text{ ppb or } 670 \text{ µg/m}^3 \text{ (rounded to two significant figures)}$$

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

The $^{chronic}ESL_{threshold(nc)}$ of 57 ppb (200 µg/m^3) for n-hexane is based on the chronic ReV of 190 ppb (670 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 9).

Table 9. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Values and Descriptions
Study	Chang et al. (1993)
Study Population	56 workers from an offset printing factory
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Peripheral neuropathy
POD_{oc}	132 ppm (LOAEL)
Exposure Duration	12 h/d, 6 d/wk, 2.6 years (mean)
POD_{HEC}	57 ppm
Total UFs	300
Interspecies UF	NA
Intraspecies UF	10
LOAEL UF	10
Incomplete Database UF *Database Quality*	3 Medium to high
Chronic ReV (HQ = 1)	**670 µg/m³ (190 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**200 µg/m³ (57 ppb)**

4.3 Carcinogenic Potential

There is only one inhalation study available on the carcinogenic effects of hexane in animals. Daughtrey et al. (1999) reported findings from a 2-year carcinogenicity studies with commercial hexane in F344 rats and B6C3F1 mice. In this study, fifty animals/sex/group/species were exposed to a commercial hexane preparation at targeted concentrations of 0, 900, 3,000, or 9,000 ppm (target concentrations), 6 h/d, 5 d/wk for 2 years. The commercial hexane consisted of 51.5% n-hexane, 16% methylcyclopentane, 16.1% 3-methylpentane, 12.9% 2-methylpentane, 3.3% cyclohexane, and trace amounts of other hydrocarbons. There was no n-hexane-related tumor formation at any tissue site in F344 rats. There was a statistically significant, dose-related increase in the incidence of hepatocellular neoplasms in the livers of female mice exposed to 9,000 ppm compared with controls. There was also an increased incidence of pituitary adenomas in female mice exposed to 900 ppm or higher. However, the USEPA indicated that the increased tumor incidence was of borderline statistical significance and was not present in treated male mice or in either sex of F344 rats exposed to commercial hexane under the same

conditions. Based on a lack of data concerning carcinogenicity in humans and animals, the USEPA has classified hexane as a Group D, not classifiable as to human carcinogenicity (USEPA 2005).

4.4 Welfare-Based Chronic ESL

There is insufficient data to establish an effect on vegetation as a result of chronic exposure to hexane.

4.5 Long-Term ESL and Values for Air Monitoring Data Evaluations

4.5.1 n-Hexane

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

- chronic ReV = 670 µg/m^3 (190 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 200 µg/m^3 (57 ppb)

The long-term ESL for air permit evaluations is 200 µg/m^3 (57 ppb) (Table 1). The chronic ReV of 670 µg/m^3 (190 ppb) is used for evaluation of monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5.2 Other hexane Isomers

No subchronic/chronic toxicity data were available describing the potential chronic toxicity of other hexane isomers. The critical effect for chronic exposure to n-hexane is peripheral neuropathy and the metabolite of n-hexane (2,5-hexanedione) is responsible for the unique neurotoxic properties of n-hexane. It is not certain that other hexane isomers can be potential neuropathic hexane. ACGIH (2001) indicates that it seems unlikely that all the hexanes would follow the same metabolic route in the body as n-hexane, in view of the marked variations in structure of the molecule. The TCEQ conservatively considers all hexane isomers are potential neuropathic alkanes. For the purpose of health effects evaluations for ambient air monitoring data, the chronic ReV value of 670 µg/m^3 (190 ppb) for n-hexane will be used as a surrogate. For the purpose of health effects evaluations for air permit applications, the $^{chronic}ESL$ of 200 µg/m^3 (57 ppb), as n-hexane, will be used.

4.6 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)

The chronic inhalation observed adverse effect level ($^{chronic}IOAEL$) of 130 ppm for n-hexane was based on the $LOAEL_{HEC}$ of 132 ppm for peripheral neuropathy observed from the human study (Chang et al. 1993). No exposure duration was adjusted. Effects occurred in some workers and the $^{chronic}IOAEL$ 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 intraspecies differences in sensitivity. The ^{chronic}IOAEL level is provided for informational purposes only (TCEQ 2015a). The ^{chronic}IOAEL for n-hexane is:

- n-Hexane ^{chronic}IOAEL = 130 ppm (460 mg/m^3) (rounded to 2 significant figures)

The margin of exposure between the ^{chronic}IOAEL (130 ppm) and the chronic ReV (0.19 ppm) for n-hexane is a factor of ~684.

Chapter 5 References

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Appendix Determination of Chronic POD_{HEC} for LOAELs

A.1 POD for LOAEL from the Chang et al. (1993) Study

A.1.1 Exposure Duration Adjustments

The occupational POD (POD_{oc}) of 132 ppm for LOAEL was adjusted to a POD that is representative of a human equivalent concentration applicable to the general population (POD_{HEC}).

$$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_{h}) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

where: VE_{ho} = occupational ventilation rate for an eight-hr day (10 m^3/day)
VE_{h} = non-occupational ventilation rate for a 24-hr day (20 m^3/day)
$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)
$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

In the formula listed above, the default occupational ventilation rate of 10 m^3/d was determined for an 8-h workday and the workers in the Chang et al. (1993) study worked 12 h/d. However, based on scientific judgment, use of the default ventilation rate based on an 8-h workday was considered conservative for use in the derivation of POD_{HEC}.

$$POD_{HEC} = 132 \text{ ppm} \times (10/20) \times (6/7) = 57 \text{ ppm}$$

A.2 POD for LOAEL from the Miyagaki (1967) Study

A.2.1 Exposure Duration Adjustments

The POD of 250 ppm (LOAEL) was conducted for 24 h/d, 6 d/week for one year. No exposure duration adjustment was conducted. Thus, the POD_{ADJ} from the 24-h POD is 250 ppm.

A.2.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

As described in Section 3.2.6.2 of this DSD, because the ratio of the animal-to-human partition coefficients (1.72/0.8 = 2.15) is greater than one, a default value of one is used as the RGDR. The resulting POD_{HEC} for the LOAEL-based from the POD_{ADJ} of 250 ppm is 250 ppm for n-hexane.