



Development Support Document
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Pentane, All Isomers

CAS Registry Numbers:

n-Pentane: 109-66-0

Isopentane: 78-78-4

Neopentane: 463-82-1

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES.....	II
LIST OF FIGURES.....	II
ACRONYMS AND ABBREVIATIONS.....	III
CHAPTER 1 SUMMARY TABLES.....	1
CHAPTER 2 MAJOR SOURCES OR USES, AND AMBIENT AIR CONCENTRATIONS.....	5
3 ACUTE EVALUATION.....	5
3.1 PHYSICAL/CHEMICAL PROPERTIES	5
3.2 HEALTH-BASED ACUTE RE _V AND ^{ACUTE} ESL.....	5
3.2.1 <i>Key Study</i>	6
3.2.1.1 TNO (1999) Report (Lammers et al. 2011) Study.....	6
3.2.2 <i>Supporting Animal Studies</i>	7
3.2.2.1 McKee et al. (1998) Study	7
3.2.2.2 Glowa (1991) Study	7
3.2.2.3 Frantik et al. (1994) Study.....	8
3.2.2.4 Halder et al. (1986) Study	9
3.2.2.5 Stadler et al. (2001) Study.....	9
3.2.2.6 Swann et al. (1974) Study	10
3.2.3 <i>Reproductive/Developmental Toxicity Studies</i>	12
3.3 MODE OF ACTION (MOA) ANALYSIS AND DOSE METRIC.....	12
3.4 POD FOR THE KEY STUDIES AND CRITICAL EFFECT	13
3.5 DOSIMETRIC ADJUSTMENTS.....	13
3.5.1 <i>Exposure Duration Adjustments</i>	13
3.5.2 <i>Default Dosimetry Adjustments from Animal-to-Human Exposure</i>	13
3.5.3 <i>Adjustments of the POD_{HEC}</i>	14
3.5.4 <i>Health-Based Acute Re_V and ^{acute}ESL</i>	14
3.6 WELFARE-BASED ACUTE ESLs	15
3.6.1 <i>Odor Perception</i>	15
3.6.2 <i>Vegetation Effects</i>	16
3.7 ACUTE RE _V AND ^{ACUTE} ESL.....	16
CHAPTER 4 CHRONIC EVALUATION.....	16
4.1 NONCARCINOGENIC POTENTIAL	16
4.1.1 <i>Physical/Chemical Properties</i>	16
4.1.2 <i>Human Study</i>	17
4.1.3 <i>Key Animal Study- Frontalli et al. (1981)</i>	17
4.1.4 <i>Supporting Animal Studies</i>	18
4.1.4.1 Aranyi et al. (1986) Study	18
4.1.4.2 Takeuchi et al. (1981) Study	18
4.1.4.3 McKee et al. (1998) Study	19
4.1.5 <i>Reproductive/Developmental Toxicity Studies</i>	19
4.1.6 <i>MOA Analysis and Dose Metric</i>	19
4.1.7 <i>POD for the Key Study and Critical Effect</i>	20
4.1.8 <i>Dosimetric Adjustments</i>	20
4.1.8.1 Exposure Duration Adjustments	20
4.1.8.2 Default Dosimetry Adjustments from Animal-to-Human Exposure	20
4.1.9 <i>Adjustments of the POD_{HEC}</i>	20

4.1.10 Health-Based Chronic ReV and ^{chronic}ESL_{nonlinear(nc)} 21

4.2 CARCINOGENIC POTENTIAL 23

4.3 WELFARE-BASED CHRONIC ESL 23

4.4 CHRONIC REV AND ^{CHRONIC}ESL_{NONLINEAR(NC)} 23

CHAPTER 5 REFERENCES 23

5.1 REFERENCES CITED IN THE DSD 23

LIST OF TABLES

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

Table 2. Air Permitting Effects Screening Levels (ESLs) 2

Table 3. Chemical and Physical Data 3

Table 4. Summary of Acute and Subacute Animal Inhalation Studies 10

Table 5. Derivation of the Acute ReV and ^{acute}ESL 15

Table 6. Derivation of the Chronic ReV and ^{chronic}ESL_{nonlinear(nc)} 22

LIST OF FIGURES

Figure 1. n-Pentane Health Effects and Regulatory Levels 4

Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ACTH	adrenocorticotropin
⁰ C	degrees centigrade
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 _{generic}	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
^{acute} ESL _{odor}	acute odor-based Effects Screening Level
^{acute} ESL _{veg}	acute vegetation-based Effects Screening Level
^{chronic} ESL _{linear(c)}	chronic health-based Effects Screening Level for linear dose response cancer effect
^{chronic} ESL _{linear(nc)}	chronic health-based Effects Screening Level for linear dose response noncancer effects
^{chronic} ESL _{nonlinear(c)}	chronic health-based Effects Screening Level for nonlinear dose response cancer effects
^{chronic} ESL _{nonlinear(nc)}	chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
^{chronic} ESL _{veg}	chronic vegetation-based Effects Screening Level
EPS	expandable polystyrene
EU	European Union
F	exposure frequency, days per week
FOB	Functional observational battery
GC	gas chromatography
GD	gestation day
GLP	good laboratory practice

Acronyms and Abbreviations	Definition
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
HPA	hypothalamic-pituitary-adrenal
HQ	hazard quotient
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
μg	microgram
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number
NAC	National Advisory Committee
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OSHA	Occupational Safety and Health Administration
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

Acronyms and Abbreviations	Definition
PUR	polyurethane
ReV	reference value
RGDR	regional gas dose ratio
SA	surface area
SD	Sprague-Dawley
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
V _E	minute volume

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 all isomers of pentane (n-pentane, isopentane, and neopentane). Please refer to the Air Monitoring Comparison Values Document (AMCV Document) available at <http://www.tceq.state.tx.us/implementation/tox/AirToxics.html> for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on n-pentane, isopentane, and neopentane's physical/chemical data.

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

Short-Term Values	Concentration	Notes
Acute ReV	200,000 $\mu\text{g}/\text{m}^3$ (68,000 ppb) Short-Term Health	Critical Effect: Free-standing NOAEL due to lack of clinical, motor activity and neurobehavioral effects observed in rats in key study
^{acute} ESL _{odor}	4,100 $\mu\text{g}/\text{m}^3$ (1,400 ppb) for n-pentane 3,800 $\mu\text{g}/\text{m}^3$ (1,300 ppb) for isopentane Odor	50% detection threshold
^{acute} ESL _{veg}	- - -	No data found
Long-Term Values	Concentration	Notes
Chronic ReV	24,000 $\mu\text{g}/\text{m}^3$ (8,000 ppb) Long-Term Health	Critical Effect(s): Free-standing NOAEL due to lack of neuromuscular function and morphological giant axonal degradation observed in rats in key study
^{chronic} ESL _{linear(c)} ^{chronic} ESL _{nonlinear(c)}	- - -	Inadequate information to assess carcinogenic potential
^{chronic} ESL _{veg}	- - - Long-Term Vegetation	No data found

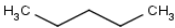
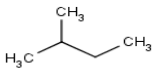
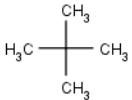
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute} ESL [1 h] (HQ = 0.3)	59,000 µg/m ³ (20,000 ppb) ^a	Critical Effect: Free-standing NOAEL due to lack of clinical, motor activity and neurobehavioral effects observed in rats in key study
^{acute} ESL _{odor}	4,100 µg/m ³ (1,400 ppb) for n-pentane 3,800 µg/m ³ (1,300 ppb) for isopentane Short-Term ESL for Air Permit Reviews	50% detection threshold
^{acute} ESL _{veg}	---	No data found
Long-Term Values	Concentration	Notes
^{chronic} ESL _{nonlinear(nc)} (HQ = 0.3)	7,100 µg/m ³ (2,400 ppb) ^b Long-Term ESL for Air Permit Reviews	Critical Effect: Free-standing NOAEL due to lack of neuromuscular function and morphological giant axonal degradation observed in rats in key study
^{chronic} ESL _{linear(c)} ^{chronic} ESL _{nonlinear(c)}	---	Inadequate information to assess carcinogenic potential
^{chronic} ESL _{veg}	---	No data found

a Based on the acute ReV of 200,000 µg/m³ (68,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

b Based on the chronic ReV of 24,000 µg/m³ (8,000 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-Pentane	Isopentane	Neopentane	Reference
Molecular Formula				ChemIDPlus
Structural Formula	$\text{H}_3\text{C}-(\text{CH}_2)_3-\text{CH}_3$	$(\text{H}_3\text{C})_2\text{CHCH}_2\text{CH}_3$	$\text{C}(\text{CH}_3)_4$	ACGIH (2001)
Molecular Weight	72.15	72.15	72.15	ACGIH (2001)
Physical State	Liquid	Liquid	Gas/Liquid	ACGIH (2001)
Color	Colorless	Colorless	Colorless	ACGIH (2001)
Odor	Sweet or gasoline-like odor	Gasoline-like odor	---	ACGIH (2001)
CAS Registry Number	109-66-0	78-78-4	463-82-1	ACGIH (2001)
Synonyms	Amyl hydride; Pentane	1,1,2- Trimethylethane; 2-Methylbutane; Dimethylethyl- methane	1,1,1- Trimethylethane; 2,2- Dimethylpropane;	ChemIDPlus
Water Solubility	Practically insoluble (38 mg/L @ 25°C)	Insoluble	Insoluble	ACGIH (2001)
Log K_{ow}	3.39	2.72	3.11	ChemIDPlus
Vapor Pressure	514 mm Hg @ 25°C	689 mm Hg @ 25°C	1290 mm Hg @ 25°C	ChemIDPlus
Vapor Density (air = 1)	2.48	---	---	ChemIDPlus

Parameter	n-Pentane	Isopentane	Neopentane	Reference
Density	0.6262 @ 20°C	0.6197 @ 20°C	0.591 @ 20°C	ACGIH (2001)
Melting Point	-129.7°C	-159.9°C	-16.6°C	ACGIH (2001)
Boiling Point	36.1°C	27.8°C	9.5°C	ACGIH (2001)
Conversion Factors @25°C	1 µg/m ³ = 0.34 ppb 1 ppb = 2.95 µg/m ³	1 µg/m ³ = 0.34 ppb 1 ppb = 2.95 µg/m ³	1 µg/m ³ = 0.34 ppb 1 ppb = 2.95 µg/m ³	TCEQ 2006

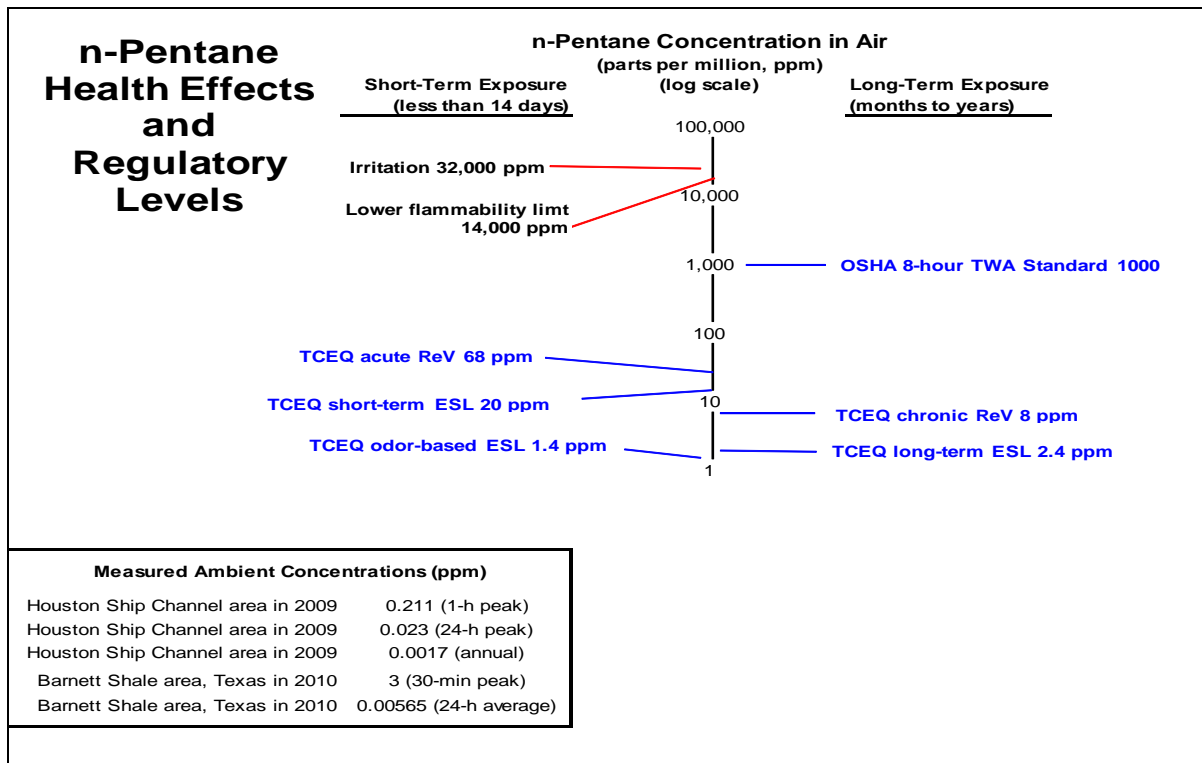


Figure 1. n-Pentane Health Effects and Regulatory Levels

This figure compares n-pentane's acute toxicity values (acute ReV, odor-based ESL, and health-based, short-term ESL) and chronic toxicity values (chronic ReV and long-term ESL) found in Tables 1 and 2 to OSHA's occupational values and observed health effects.

Chapter 2 Major Sources or Uses, and Ambient Air Concentrations

General pentane (hereafter, pentane) is a colorless, volatile and flammable liquid with a sweet or gasoline-like odor. Pentane consists of three isomers: n-pentane (the most important isomer), isopentane, and neopentane. n-Pentane is a constituent of crude oil and a component of the condensate from natural gas production. It is primarily obtained by fractional distillation of a petroleum stream (generally light virgin naphtha) obtained from the processing of crude oil. n-Pentane is used as a component of gasoline blends, as an aerosol propellant, in low temperature thermometers, as a blowing agent for foams (e.g. expandable polystyrene (EPS) and polyurethane (PUR)), and as a solvent (EU 2003). Isopentane is also used as a blowing agent, and neopentane is used in the manufacture of butyl rubber (ACGIH 2001).

Pentane can be released into the air from industrial production plants. It is also released to the environment during its use in the EPS industry, PUR industry, or polymer production, and use in adhesives and glues. Pentane released to the environment is expected to volatilize to the atmosphere, where it will undergo photochemical oxidation reactions with hydroxyl radicals (USEPA 1987). Annual pentane mean concentrations of 37.7 and 82 $\mu\text{g}/\text{m}^3$ have been reported in New York City (Altwicker et al. 1980, as cited in EU 2003). Hazardous Substance Databank (HSDB 2010) reports that the maximum and average concentration of 676 samples for n-pentane taken in 1977 at a site in Houston, Texas was 190 and 27 ppb, respectively. Rural areas have much lower concentrations. The maximum ambient concentration for five rural locations in North Carolina has been reported to range from 1.6 to 26.2 ppb. Concentration measured at the Jones State Forest in rural Texas was 11.1 ppb (Saila 1979, as cited in HSDB 2010). In 2009, a Houston Ship Channel ambient air monitoring site that collects both 1-h (autoGC) and 24-h (canister) n-pentane levels reported peak concentrations of 211 and 23 ppb, respectively. The annual average concentration for the more than 7,000 1-h samples was 1.4 ppb and 1.7 ppb for the 52 canister samples collected in 2009. In the spring of 2010, peak 30-min and 24-h average ambient concentration of 3,000 and 5.65 ppbv, respectively, have been measured by AutoGC in the Barnett Shale area near Dish, Texas. Please refer to Figure 1.

3 Acute Evaluation

3.1 Physical/Chemical Properties

Pentane is a colorless, highly volatile, and flammable liquid with a gasoline-like odor. It exists in three isomeric forms: n-pentane (the most importantly used isomer), isopentane (most volatile isomer), and neopentane. Neopentane forms tetragonal crystals upon solidification (ACGIH 2001). The main chemical and physical properties of these three isomers are summarized in Table 3.

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

Pentane has a low acute respiratory toxicity. Inhalation of extremely high concentrations of pentane causes depression of the central nervous system (CNS) and irritation of the nose and throat. No human studies are available concerning acute effects of pure pentane. Acute effects

are considered similar to that of other saturated aliphatic hydrocarbons of similar length (C₃-C₈) (EU 2003). In the only human inhalation study, no mucous membrane irritation or other symptoms, or vertigo (dizziness) were experienced by three to six volunteers exposed to up to 5,000 ppm pentane (76.5% n-pentane, 20.8% isopentane; 1.3% butanes and 1.4% hexanes) for 10 minutes (min) (Patty and Yant 1929). This study, however, is considered insufficient for the development of an acute reference value (ReV) and effects screening level (ESL) because the physiological response reported by the tested subjects during the odor intensity tests was subjective and the number of tested subjects was small. Based on animal studies, high concentrations of n-pentane (e.g., above the lower explosive limit (LEL) of 14,000 ppm) may cause temporary irritation of the nose and throat and depression of CNS with symptoms such as headache, nausea, dizziness, drowsiness, anesthesia, and confusion (Galvin and Marashi 1999). Most reported toxicity studies were conducted for n-pentane and reports are very limited for other isomers of pentane. 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). Similar results were reported by Stoughton and Lamson (1936) that neopentane was less anesthetic and lethal than isopentane, which was less anesthetic and lethal than pentane. One reason why iso- and neo-pentane could be less anesthetic and lethal than n-pentane is that they are less well absorbed (Dahl et al. 1988).

Therefore, the TD will use the health-based acute and chronic ReVs and ESLs developed for n-pentane as a surrogate for all isomers of pentane.

3.2.1 Key Study

Information from human studies regarding the acute toxicity of pentane is limited and insufficient for the development of the ReV and ESL. Therefore, animal studies were used to develop the acute ReV and ESL. Animal data indicate that acute and subacute pentane exposures can elicit anesthesia, CNS depression, neurobehavioral effects, and respiratory irritation. However, few studies have provided exposure dose-response data to identify a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL). Animal studies that investigated n-pentane, including Glowa (1991), Stadler et al. (2001), McKee et al. (1998), Frantik et al. (1994), Swann et al. (1974), and TNO (1999, report No. V98.791, as cited in EU 2003, now is a part of Lammer et al. 2011), have provided the NOAEL and/or LOAEL values used to develop the acute ReV and ESL. The TD chose the report by TNO (1999, report No. V98.791; Lammers et al. 2011) as the key study because it was a well conducted study. Other animal studies were used as supporting studies (See Section 3.2.2 below).

3.2.1.1 TNO (1999) Report (Lammers et al. 2011) Study

In a report by TNO (1999, report No. V98.791; Lammers et al. 2011), two different studies on behavioral effects of n-pentane in rats were performed in accordance with good laboratory practice (GLP) conditions. In both studies, male WAG/RijCHBR rats (8 rats/group) were exposed to air (control), 2,000, 6,500, or 20,000 mg/m³ n-pentane (target concentrations) 8 h/day (d) for 3 d. The highest exposure level used in the pentane study (20,000 mg/m³) is

approximately half of the lower explosive level (LEL) and the highest concentration considered safe to test. The mean analytical exposure concentrations were 1,985, 6,318, and 19,872 mg/m³ (675, 2,148, and 6,756 ppm). In the first study, motor activity and neurobehavioral function (using a standardized functional observational battery (FOB)) were evaluated. The results showed that exposure to n-pentane did not induce any dose-related effects on FOB or motor activity measures. In the second study, cognitive performance was evaluated using a discrete-trial, two-choice visual discrimination performance testing. Mild and reversible changes in measures of learned performance were reported. At 1,985 and 6,318 mg/m³, a mild and reversible difference in measures of performance speed (significantly larger latencies) was reported during or after 3 consecutive 8-h exposures, compared to the control group. However, exposure to 19,872 mg/m³ did not induce exposure-related neurobehavioral effects. The post-exposure test indicated that there were no effects due to n-pentane one day after the end of exposure. The authors indicated that because the uptake and elimination of n-pentane from the CNS is relatively rapid, the brain concentrations of n-pentane were reduced during the post-exposure neurobehavioral tests. In both studies, no changes in body weights or remarkable clinical signs between the groups were reported. A free-standing NOAEL of 19,872 mg/m³ (6,756 ppm) was identified from both studies and was used as point of departure (POD) to develop the acute ReV and ^{acute}ESL.

3.2.2 Supporting Animal Studies

3.2.2.1 *McKee et al. (1998) Study*

McKee et al. (1998) reported a 5-d inhalation range-finding study for the 90-d study which was carried out at the Exxon Biomedical Sciences (EBS) Toxicology Laboratory. Groups of 10 Sprague-Dawley rats (5 males and 5 females) were exposed by whole-body inhalation, 6 h/d, for 5 d to 0 (control), 5,000, 10,000, or 20,000 mg/m³ n-pentane (nominal concentrations). The mean analytical exposure concentrations were 5,446, 10,680 and 21,418 mg/m³ (1,813, 3,556 and 7,132 ppm) as measured by on-line gas chromatography (GC). Parameters evaluated included survival, body weights, clinical observations, and gross post-mortem examinations. No adverse effects with respect to clinical signs, including mortality and obvious toxic signs during the first and last hours of exposure, body weight gain, or post-mortem findings were observed. A free-standing NOAEL of approximately 21,418 mg/m³ (7,132 ppm) (mean analytical concentration) was identified from this study. The 5-d exposure NOAEL was consistent with that identified from the 3-d exposure key study by TNO (1999), or Lammers et al. (2011).

3.2.2.2 *Glowa (1991) Study*

This study examined the ability of n-pentane to impair performance (neurobehavioral effects) and to stimulate the hypothalamic-pituitary-adrenal (HPA) axis (neuroendocrine effects) in adult male CD-1 mice (35-40 g). Four to six mice per group were exposed to each concentration. Cumulative concentration-effect functions were obtained by incrementally increasing exposure concentration from 100 ppm (nominal concentrations), and until response was abolished. Impaired performance was assessed by studying operant response maintained under a fixed interval (FI) 60-second schedule of milk presentation. Individual concentration effect functions

were obtained by comparing pre-exposure (control) levels of response to response after 30-min of exposure of incrementally increased n-pentane concentrations. Recovery was determined 30 min following removal from exposure. The results showed that concentrations less than 10,000 ppm n-pentane slightly increased the response, whereas larger concentrations decreased response in a concentration-related manner with 30,000 and 56,000 ppm decreasing response approximately 50% and 100%, respectively. Response recovered fully 30 min following ceasing exposure to 56,000 ppm n-pentane. Rate-decreasing potency (EC_{50}) was 36,130 ppm. The level of 10,000 ppm can be considered a NOAEL for transient behavioral impairment. The NOAEL is higher than that identified from the key study and thus, was not used as the POD to develop the acute ReV and ^{acute}ESL.

The effect on HPA axis activation was studied by exposing mice (6 mice per concentration) to n-pentane (100 to 10,000 ppm) for 30 min. Immediately after exposure ceased, animals were sacrificed and the adrenocorticotropin (ACTH) levels in serum were measured. The increase in serum ACTH levels were in a dose-related manner, although large increases were not obtained in this study until after exposure to 10,000 ppm n-pentane. The ACTH level was the same from 100 to 1,000 ppm (approximately 80% of control). Between 1,000 ppm and 10,000 ppm, there are no distinct data points that indicate a clear effect of ACTH levels. The ACTH level increased slightly at concentrations up to 3,000 ppm, then it increased approximately 1,100% of control at 10,000 ppm. The level of 3,000 and 10,000 ppm may be considered a NOAEL and LOAEL, respectively, for HPA activation. However, no statistical significance analysis were determined and thus, the effects of neuroendocrine as measured by HPA activation may not be adverse. Therefore, the NOAEL of 3,000 ppm for HPA activation was not selected as POD to develop the acute ReV and ^{acute}ESL.

3.2.2.3 Frantik et al. (1994) Study

Frantik et al. (1994, as cited in EU 2003) studied acute neurotropic effects of n-pentane in male Wistar rats (0.5-1 year old) and female H-strain mice (2-4 months old) exposed whole-body to n-pentane for 2 h (mice) or 4 h (rats), four animals per exposure group. Neurotropic effects were measured as inhibition of propagation and maintenance of the electrically evoked seizure discharge. The method used has a high sensitivity since generation, propagation, and maintenance of the seizure discharge require repeated passages through serially connected neurons of reverberating circuits. The lowest effective concentration (EC_{10}), i.e., concentration slowing the propagation or shortening the duration of the seizures by 10%, in this study was reported to be 62,790 mg/m^3 (21,000 ppm) for rats and 70,265 mg/m^3 (23,500 ppm) for mice. The ability of n-pentane to impair performance in mice revealed an EC_{50} of 108,030 mg/m^3 (36,130 ppm). Neurotropic effects of n-pentane were observed in rats and mice exposed whole-body to 62,790 and 70,265 mg/m^3 (21,000 and 23,500 ppm, analytical concentrations) n-pentane, respectively. A LOAEL (EC_{10}) of 62,790 mg/m^3 (21,000 ppm) was identified from this study.

3.2.2.4 Halder et al. (1986) Study

Halder et al. (1986) conducted a 3-week inhalation study to evaluate the nephrotoxicity of a mixture of C₄/C₅ hydrocarbons containing 25 weight % each of n-pentane, isopentane, n-butane and isobutane. Groups of 36-45 d old Sprague-Dawley (SD) rats (10/sex/group) were exposed to 0 (control), 116 mg/m³ (44 ppm), 1,150 mg/m³ (432 ppm) or 11,800 mg/m³ (4,437 ppm) (time-weighted average analytical concentrations) C₄/C₅ hydrocarbon mixture for 6 h/d, 5 d/week for 3 weeks. All animals were sacrificed immediately after exposure termination. The study specifically focused on the kidneys to identify those lesions that are recognized to represent effects of hydrocarbon-induced nephropathy in male rats. During the study, the rats showed no clinical signs of distress, and no treatment-related pathological lesions were noted upon either gross or microscopic examination. The results of this study suggest that short-term exposures to a mixture of C₄/C₅ hydrocarbons produced no kidney damage in male SD rats – the most sensitive sex and animals to this effect, at concentrations up to 11,800 mg/m³ (4,437 ppm). The level is considered a NOAEL for the mixture of C₄/C₅ hydrocarbons. The results of this mixture study are consistent with the studies of pure n-pentane exposures.

3.2.2.5 Stadler et al. (2001) Study

Stadler et al. (2001) conducted a preliminary range-finding inhalation study for the 2-week study in which four male Crl:CD rats (44 d old) were exposed to 10,000 ppm n-pentane 6 h/d for 4 d. No clinical signs of toxicity were observed. The level of 10,000 ppm was then selected as the highest exposure level for their main study and could be considered a free-standing NOAEL for a 4-d acute study. The NOAEL is higher than that identified from the TNO (1999) or Lammers et al. (2011) key study and thus, was not used as the POD to develop the acute ReV and ^{acute}ESL.

In the main study, groups of 10 male rats were exposed, 6 h/d, 5 d/week for two weeks to either 0 (control), 1,000, 3,000, or 10,000 ppm n-pentane (nominal concentrations). The respective mean analytical concentrations were 0, 990, 3,100 and 9,900 ppm. Five rats per group were killed following the 10th exposure, and the remaining five rats per group were killed after a 14-day post-exposure recovery period. Parameters evaluated were clinical signs of toxicity, functional behavior, body weights, clinical pathology, and gross and microscopic pathology including organ weights. No clinical signs of toxicity were reported, and body weight and performance on behavioral tests were not altered in all exposure groups. Statistically significant increases in serum calcium and phosphorus concentrations were seen in rats exposed at 3,000 and 10,000 ppm exposure groups compared to controls. However, these changes were reversible during the two-week recovery period. No other clinical pathology changes were reported, and no n-pentane-related tissue pathology was seen in any of the treatment groups. The combination of increased levels of serum calcium and phosphorus was considered a potentially adverse effect since it indicated that alterations in mineral metabolism or homeostasis might have occurred. However, the authors stated that to ascribe these effects as treatment-related would be a fairly conservative position (EU 2003). Furthermore, in a 90-day inhalation toxicity study by McKee et al. (1998), no effects on serum chemistry, and no resulting adverse effects in any of the test animals exposed with concentrations up to 20,000 mg/m³ (6,800 ppm) were reported (see

Section 4.1.4.3). Thus, the toxicological significance of the serum chemistry data reported by Stadler et al. (2001) was not used as the POD to develop an acute ReV and ^{acute}ESL.

3.2.2.6 Swann et al. (1974) Study

Swann et al. (1974) studied the respiratory irritating properties of n-pentane (99% pure) in male Swiss mice (25 g). Four animals were exposed head-only for 5 min at each of the following concentrations of n-pentane: 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, 64,000 and 128,000 ppm (nominal concentrations). The respiratory rate, depth, and configuration were counted and recorded for 15-second intervals while the animals were inhaling n-pentane. This method was described by Alarie (1966, as cited in Swann et al. 1974). Concentrations up to 16,000 ppm produced no irritation or anesthesia. At 32,000 ppm, periodic body movements were observed during the exposure, which indicate effects of irritation before the animals became lightly anesthetized during the recovery period. However, the investigators did not actually observe irritation but rather sporadic body movements which they interpreted as irritation. At 64,000 ppm, there was deeper anesthesia with considerably more body movement than at 32,000 ppm during the 5-min exposure period. At 128,000 ppm a deep anesthesia was observed, and in one out of four mice respiratory arrest occurred. A NOAEL of 16,000 ppm for periodic body movements and a NOAEL of 32,000 ppm for anesthesia were identified from this study. Since the exposure duration was only 5 min, the NOAELs were not used as a POD to develop the acute ReV and ^{acute}ESL. The results of these acute and subacute animal studies are summarized in Table 4 below.

Table 4. Summary of Acute and Subacute Animal Inhalation Studies

Study	Animal Strain	Exposure Duration	Exposure Concentrations	NOAEL	LOAEL	Response at LOAEL
TNO (1999); Lammers et al. (2011) Key Study	Male WAG/RijCHBR Rats	8 h/d for 3 d	air (control), 1,985, 6,318, and 19,872 mg/m ³ (675, 2,148, and 6,756 ppm)	19,872 mg/m ³ (6,756 ppm)	--	Endpoints evaluated: motor activity and neurobehavioral function, and cognitive performance
McKee et al. (1998)	Sprague-Dawley Rats	6 h/d, for 5 d	0 (control), 5,446, 10,680 and 21,418 mg/m ³ (1,813, 3,556 and 7,132 ppm)	21,418 mg/m ³ (7,132 ppm)	--	Endpoints evaluated: Survival, body weights, clinical observations

Study	Animal Strain	Exposure Duration	Exposure Concentrations	NOAEL	LOAEL	Response at LOAEL
Glowa (1991)	Male CD-1 Mice	30 min	100 to 10,000 ppm	10,000 ppm	30,000 ppm	Impair performance (neurobehavioral effects)
				3,000 ppm	10,000 ppm	Stimulate the hypothalamic-pituitary-adrenal (HPA) axis (neuroendocrine effects)
Swann et al. (1974)	Male Swiss Mice	5 min	1,000, 2,000, 4,000, 8,000, 16,000, 32,000, 64,000 and 128,000 ppm	16,000 ppm	32,000 ppm	Effects of respiratory irritation (body movements)
				32,000 ppm	64,000 ppm	Effects of anesthesia
Stadler et al. (2001)	Male CrI:CD Rats	6 h/d, 5 d/week for 2 weeks	0 (control), 1,000, 3,000, or 10,000 ppm	1,000 ppm	3,000 ppm	Increases in serum calcium and phosphorus concentrations
Frantik et al. (1994)	Male Wistar Rats and Female H-strain Mice	2 h or 4 h	21,000 ppm for Rats, and 23,500 ppm for Mice	--	21,000 ppm for Rats, and 23,500 ppm for Mice	Inhibition of propagation and maintenance of the electrically evoked seizure discharge (neurotropic effects)
Halder et al. (1986)	Sprague-Dawley Rats	6 h/d, 5 d/week for 3 weeks	0 (control), 44 ppm, 432 ppm or 4,437 ppm of C4/C5 hydrocarbon mixture contains 25% n-pentane	4,437 ppm	--	Nephrotoxicity was evaluated

3.2.3 Reproductive/Developmental Toxicity Studies

No information on the potential of pentane to cause developmental toxicity in humans is available.

A preliminary limited reproductive and developmental toxicity study was conducted in rats by Hurtt and Kennedy (1999). Groups of 7-8 pregnant rats were exposed by inhalation to 0 (control), 1,000, 3,000 and 10,000 ppm (nominal concentrations) n-pentane, 6 h/d, during gestation days (GD) 6-15. Maternal body weights, clinical signs and food consumption were measured; fetuses were weighed and examined for gross external development. Skeletal and internal organ evaluations, however, were not performed. No adverse effects on reproductive parameters were observed in either the maternal or fetal rats in all exposed groups. Fetal weights tended to be slightly lower in all test groups but were not statistically significant ($P > 0.05$) and there was no evidence of a dose-response trend. Based on these findings, the authors did not conduct a full-scale developmental toxicity study and concluded that it is unlikely that the fetal rat will be adversely affected by n-pentane exposure at levels up to 10,000 ppm. A NOAEL of 10,000 ppm for reproductive/developmental effects was identified from this study. The free-standing NOAEL of 10,000 ppm for reproductive/developmental toxicity in rats was not used as a POD, since protecting against CNS depression, respiratory irritation, and neurobehavioral effects would protect against reproductive/developmental effects.

An oral gavage developmental toxicity study was conducted in the EBS study. Groups of 25 pregnant CrI:CDBR SD rats (243-316 g) were administered once daily via oral gavage at doses of 100, 500, 750, and 1,000 mg/kg n-pentane during the period of major organogenesis, GD 6-15. Maternal toxicity was not evident at any dose level tested. No statistically significant differences in mean body weight, body weight change, uterine weight, corrected body weight, or uterine implantation data between treated and control dams were observed. In addition, no adverse clinical/post-mortem signs, no evidence of growth retardation or increased fetal death, and no statistically significant differences in total or individual variations or malformations (external, visceral, or skeletal) were observed in the treated group compared to controls. The NOAEL was $\geq 1,000$ mg/kg/d for dams and offspring. The study showed that n-pentane was not a developmental toxicant in rats.

3.3 Mode of Action (MOA) Analysis and Dose Metric

Animal data indicate that n-pentane exposures can elicit anesthesia, CNS depression, respiratory irritation, alterations in mineral metabolism or homeostasis, and neurobehavioral effects. The MOAs for these effects have not been fully elucidated. Therefore, as a default, a threshold, nonlinear dose-response relationship is used. Inhaled n-pentane is not absorbed efficiently and is rapidly eliminated largely by exhalation (Dahl et al. 1988). Gas-uptake pharmacokinetic studies in rats found that an elimination half-life is approximately 0.13 h (Filser et al. 1983, as cited in Galvin and Marashi 1999, McKee et al. 1998, and Lammers et al. 2011).

Aliphatic hydroxylation is the major metabolic pathway for n-pentane. Frommer et al. (1970, as cited in Galvin and Marashi 1999) found that 2-pentanol was the major metabolite (83-89%) and 3-pentanol was a minor metabolite (11-16%) formed by rats and rabbit liver microsomes. Ketone and aldehyde metabolites and 1-pentanol were not detected. Only a minor part of the dose is excreted as metabolites in urine since the initially formed products are rapidly converted by a cytochrome P450- dependent oxidation (2- and 3-pentanol) to CO₂. Pentane is rapidly metabolized in humans via the hepatic mono-oxygenase system and by conversion to the corresponding alcohol and aldehyde (Van Rij and Wade 1987, as cited in Galvin and Marashi 1999). Considering the rapid metabolism and excretion of n-pentane, potential for tissue accumulation is expected to be low. 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.

3.4 POD for the Key Studies and Critical Effect

The 8 h/d for 3-d subacute NOAEL of 19,872 mg/m³ (6,756 ppm) for acute neurobehavioral effects identified by TNO (1999) report or Lammers et al. (2011), was used as the POD to derive the acute ReV and ^{acute}ESL.

3.5 Dosimetric Adjustments

3.5.1 Exposure Duration Adjustments

Results from key and supporting studies showed that concentration (C) alone is the dominant determinant of toxicity (see Section 3.2.1 and 3.2.2) in CNS depression, respiratory irritation, and neurobehavioral effects. In addition, the MOA information has not been fully elucidated and the elimination half-life is short. Therefore, the TD conservatively assumes there is no change in concentration (TCEQ 2006). Thus, adjustment from an exposure duration (T) > 8 h/d to 1 h/d was not performed. The POD of 19,872 mg/m³ (6,756 ppm) was directly used for the default dosimetric adjustment from an animal concentration to a human equivalent concentration (POD_{HEC}) (see Section 3.5.2).

3.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

n-Pentane is practically water insoluble. Acute exposures to n-pentane cause motor activity, neurobehavioral function, and behavioral impairment (nervous system) which are systemic rather than point-of-entry (POE) effects. In addition, the physical/chemical parameters of n-pentane indicate the potential for n-pentane to be absorbed via the lungs and widely distributed within the body. n-Pentane was therefore considered a Category 3 gas (USEPA 1994, as cited in TCEQ 2006). For Category 3 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$\text{POD}_{\text{HEC}} = \text{POD}_{\text{ADJ}} \times [(\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}}]$$

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

The measured blood/air partition coefficient in human ($(\text{H}_{\text{b/g}})_{\text{H}}$) for n-pentane is 0.38 (Perbellini et al. 1985). No measured blood/air partition coefficient in the rat ($(\text{H}_{\text{b/g}})_{\text{A}}$) is available, however, a predicted $(\text{H}_{\text{b/g}})_{\text{A}}$ of 1.48 was reported by Meulenberg and Vijverberg (2000). Because the ratio of the animal-to-human partition coefficients ($1.48/0.38 = 3.9$) is greater than one, a default value of one is used as the regional gas dose ratio (RGDR) (i.e., $(\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}}$) as recommended by the TCEQ ESL guidelines (2006). The resulting POD_{HEC} from the POD of $19,872 \text{ mg/m}^3$ (6,756 ppm) in the TNO (1999) report or Lammers et al. (2011) is 6,756 ppm.

3.5.3 Adjustments of the POD_{HEC}

The POD_{HEC} of 6,756 ppm obtained from the default dosimetric adjustment for Category 3 gases was used to set the acute ReV and ^{acute}ESL. The following uncertainty factors (UFs) were applied to the POD_{HEC} :

- a UF_{H} of 10 for intraspecies variability,
- a UF_{A} of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences, and
- a UF_{D} of 3 for uncertainty associated with an incomplete database. Although multiple animal studies were conducted and multiple animal species were used in inhalation bioassays for different toxicity endpoints, there were reproductive/developmental studies in only one species. Confidence is considered medium on the database because most of the animal studies including the key study did not show dose-response relationships in inhalation bioassays. The quality of the key rat study, however, is high, although only a free-standing NOAEL was identified.
- The total $\text{UF} = 100$.

$$\begin{aligned} \text{Acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_{\text{H}} \times \text{UF}_{\text{A}} \times \text{UF}_{\text{D}}) \\ &= 6,756 \text{ ppm} / (10 \times 3 \times 3) \\ &= 67.56 \text{ ppm} \\ &= 68,000 \text{ ppb (rounded to two significant figures)} \end{aligned}$$

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

In deriving the acute ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded

ReV was then used to calculate the ESL, and the ESL subsequently rounded. The ^{acute}ESL of 20,000 ppb (59,000 µg/m³) is based on the acute ReV of 68,000 ppb (200,000 µg/m³) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 5).

Table 5. Derivation of the Acute ReV and ^{acute}ESL

Study	TNO 1999 report or Lammers et al. 2011
Study Population	Male WAG/RijCHBR Rats , 8/group
Study Quality	High
Exposure Method	Exposure via inhalation at air (control), 1,985, 6,318, and 19,872 mg/m ³ (0, 675, 2,148, and 6,756 ppm, analytical concentrations)
Critical Effects	Free-standing NOAEL
POD	6,756 ppm (free-standing NOAEL)
Exposure Duration	8 h/d for 3d
Extrapolation to 1 h (POD _{ADJ})	6,756 ppm
POD _{HEC}	6,756 ppm
Total uncertainty factors (UFs)	100
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL-to-NOAEL UF</i>	N/A
<i>Incomplete Database UF</i>	3
<i>Database Quality</i>	Medium
Acute ReV [1 h] (HQ = 1)	200,000 µg/m³ (68,000 ppb)
^{acute}ESL [1 h] (HQ = 0.3)	59,000 µg/m³ (20,000 ppb)

3.6 Welfare-Based Acute ESLs

3.6.1 Odor Perception

Pentane has a sweet or gasoline-like odor. Nagata (2003) reported an odor detection threshold of 1.4 ppm for n-pentane and 1.3 ppm for isopentane, which were determined by the standardized methods of measuring odor. These odor detection values meet the criteria accepted by American Industrial Hygiene Association (AIHA) and USEPA (AIHA 1989 and USEPA 1992) and definition of Level 1 quality data according to the interim guidelines for setting odor-based effects screening levels (TCEQ 2010). Odor detection values defined as the highest quality level

of odor thresholds (Level 1) will be considered first in setting the $^{acute}ESL_{odor}$ values. Thus, the $^{acute}ESL_{odor}$ for n-pentane is 1,400 ppb ($4,100 \mu\text{g}/\text{m}^3$), and is 1,300 ppb ($3,800 \mu\text{g}/\text{m}^3$) for isopentane. No odor threshold value for neopentane was reported.

3.6.2 Vegetation Effects

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

3.7 Acute ReV and $^{acute}ESL$

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

- $^{acute}ReV = 200,000 \mu\text{g}/\text{m}^3$ (68,000 ppb)
- $^{acute}ESL = 59,000 \mu\text{g}/\text{m}^3$ (20,000 ppb)
- $^{acute}ESL_{odor}$ for n-pentane = $4,100 \mu\text{g}/\text{m}^3$ (1,400 ppb)
- $^{acute}ESL_{odor}$ for isopentane = $3,800 \mu\text{g}/\text{m}^3$ (1,300 ppb)

The $^{acute}ESL_{odor}$ of $4,100 \mu\text{g}/\text{m}^3$ (1,400 ppb) for n-pentane and $3,800 \mu\text{g}/\text{m}^3$ (1,300 ppb) for isopentane may be used as the odor-based air monitoring comparison values (AMCVs) for evaluation of ambient air monitoring data. The acute ReV of $200,000 \mu\text{g}/\text{m}^3$ (68,000 ppb) may be used as a health-based AMCV for evaluation of ambient air monitoring data for all pentane isomers (Table 1).

The short-term ESL for air permit evaluations is the $^{acute}ESL_{odor}$ of $4,100 \mu\text{g}/\text{m}^3$ (1,400 ppb) for n-pentane, the $^{acute}ESL_{odor}$ of $3,800 \mu\text{g}/\text{m}^3$ (1,300 ppb) for isopentane, and the $^{acute}ESL$ of $59,000 \mu\text{g}/\text{m}^3$ (20,000 ppb) for neopentane (Table 2). The $^{acute}ESL$ of $59,000 \mu\text{g}/\text{m}^3$ (20,000 ppb) (HQ = 0.3) is not used for evaluation of air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Pentane is generally quite low in chronic toxicity. Studies of effects from prolonged exposure to high concentrations of n-pentane in humans have not been reported. There has been one chronic (Frontali et al. 1981) and several subchronic inhalation studies of n-pentane reported in animals (McKee et al. 1998, Takeuchi et al. 1981, Aranyi et al. 1986). The TD used the NOAEL identified from the Frontali et al. 1981 chronic exposure study to derive chronic ReV and ESL values.

4.1.1 Physical/Chemical Properties

Physical/chemical properties for n-pentane and other isomers are discussed in Section 3.1.

4.1.2. Human Study

There is only one report related to human effects associated with n-pentane exposure. Gaultier et al. (1973, as cited in USEPA 1987, McKee et al. 1998 and EU 2003) reported five female workers who developed signs of peripheral neuropathy following exposure to a mixed solvent containing 80% n-pentane, 14% n-heptane and 6% n-hexane. Concentration and duration of exposure were not specified. Affected workers had anorexia, paresthesia, symmetrical muscle failure, asthenia, peripheral nerve damage and signs of denervation in the legs. The results were attributed to the presence of n-hexane. However, the authors questioned whether n-pentane exposure was also associated with polyneuropathy in humans. Consequently, the authors suggested that tests of n-alkanes, particularly n-pentane in rats, should be carried out, and that more careful clinical examinations to determine if n-pentane might exhibit neurotoxic properties. Two animal studies were subsequently carried out by Frontalli et al. (1981) and Takeuchi et al. (1981). The results of these studies demonstrated that n-hexane can produce peripheral neuropathy under experimental conditions. However, the studies provided no evidence that n-pentane was neurotoxic (see Section 4.1.4 below). Because there are no reports of neurotoxic effects of n-pentane in humans, and there are a number of case reports describing peripheral neuropathy in humans exposed to n-hexane, McKee et al. (1998) suggest that n-hexane was the most likely causative agent for developing peripheral neuropathy in workers exposed to the mixed solvent product. Galvin and Bond (1999) reported that shorter chain alkanes (pentane) and hexane isomers free of n-hexane fail to produce the appropriate metabolite to cause polyneuropathy or peripheral neuropathy. n-Hexane is metabolized in humans/animals to the diketone 2, 5-hexanedione, which is responsible for the peripheral nervous system damage in humans/rats. The metabolic pathway of n-pentane does not involve formation of the diketone; rather, it involves hydroxylation to pentanol (Frommer et al., as cited in Galvin and Marashi 1999) (see Section 3.3.).

4.1.3. Key Animal Study- Frontalli et al. (1981)

Frontalli et al. (1981) conducted a chronic inhalation neurotoxicity study in groups of 6-9 SD rats (230-260 g), exposed to 0 (control), and different concentrations of n-hexane (2,500 or 5,000 ppm), cyclohexane (1,500 or 2,500 ppm), 2- or 3-methylpentane (1,500 ppm), n-heptane (1,500 ppm), and n-pentane (3,000 ppm), 9 h/d, 5 d/week for 30 weeks. At weekly or monthly intervals the rats were weighed and subjected to a physiological test of neuromuscular function. The results showed that only n-hexane at 2,500 (after 30 weeks) and 5,000 ppm (after 14 weeks) gave rise to histological signs of giant axonal degeneration accompanied by a significant decrease in body weight. No such alterations were found in rats exposed to n-hexane 500 ppm (30 weeks) or 1,500 ppm (14 weeks), cyclohexane 1,500 or 2,500 ppm (30 weeks), n-heptane 1,500 ppm (30 weeks), 2- or 3-methylpentane 1,500 ppm (30 weeks), or n-pentane 3,000 ppm (30 weeks).

For rats exposed to 3,000 ppm n-pentane for 30 weeks, a significant decrease in body weight gain was noted in the two-way analysis of variance but not in the Student's *t*-test. The percent decrease for the tested animals was not quantified, therefore, the critical effect of decrease in body weight gain was not considered since it couldn't be determined whether this represented an

adverse effect. A difference in neuromuscular function observed in treated and control rats was not statistically significant. Furthermore, the test employed turned out to be scarcely effective because of high individual variability. No morphological giant axonal degradation was observed by histological examination of the nerve tissue. A free-standing NOAEL of 3,000 ppm n-pentane for neurotoxic effects was identified from this study. The chronic NOAEL was used as the POD to develop chronic ReV and ^{chronic}ESL_{nonlinear(nc)}.

4.1.4 Supporting Animal Studies

4.1.4.1 Aranyi et al. (1986) Study

In a subchronic inhalation study by Aranyi et al. (1986), 20 male and 10 female, 6-week-old Fisher rats were exposed whole-body, 6h/d, 5 d/week for 13 weeks to a 1,000 or 4,500 ppm 50:50 mixture of n-butane/n-pentane. Complete necropsies were performed at designated times, during which the presence of lesions or other abnormal conditions were assessed, and kidney and liver weights determined. The kidneys were fixed and sectioned for histopathology. The results of this study showed possible treatment-related, but not dose-related effects of the n-butane/n-pentane exposure included transient hunched posture and/or lethargy and intermittent tremor. Body weight was unaffected relative to controls at the end of the study. The renal histopathology examination revealed a treatment-related effect at the 28-day interim sacrifice in the kidneys of one group of male rats exposed to 1,000 ppm of the n-butane/n-pentane mixture relative to their associated controls. Despite this effect seen at day 28, no differences in renal histopathology were observed between treated and control groups at study termination. The renal lesions included excessive phagolysosome accumulation in the cytoplasm of epithelial cells lining the proximal convoluted tubules, degeneration/regeneration of the epithelial cells in the renal cortex, and development of granular, proteinaceous casts in the lumen of tubules located principally between the inner and outer strips of the medulla. However, these lesions occurred commonly in untreated rats, and were not present at the end of the 13-week exposure. The authors concluded that the response seen was not an indication of a frank nephrotoxic response to the n-butane/n-pentane mixture, since no differences between treated and control animals were seen at 90 d. The level of 4,500 ppm 50:50 n-butane/n-pentane mixture can be considered a free-standing NOAEL. Since the exposure was 50:50 mixture of n-butane/n-pentane and the NOAEL is higher than that identified from the Frontali et al. (1981) study and is not for pure n-pentane exposure.

4.1.4.2 Takeuchi et al. (1981) Study

In a subchronic comparative study of the neurotoxicity of n-pentane, n-hexane, and n-heptane by Takeuchi et al. (1981), groups of seven male Wistar rats (308 ± 18 g) were exposed by inhalation in chambers to 0 (control), nominal concentrations of 3,000 ppm n-pentane, n-hexane, or n-heptane 12 h/d, 7 d/week for 16 weeks. The measured concentrations were $3,080 \pm 200$, $3,040 \pm 270$ and $2,960 \pm 200$ ppm for n-pentane, n-hexane and n-heptane, respectively. The conduction velocity of tail nerves was measured to determine the functional status of the peripheral nerves. There were statistically significant differences for decreases in body weight gain and motor nerve conductivity velocity recorded from rats exposed to n-hexane and those obtained from the

control rats. Results showed that n-hexane treated rats had clinical signs of neuropathy. No particular changes in the nerve fibers and the peripheral nerve or alteration of motor conduction velocity or decreases in body weight were observed in rats exposed to n-pentane or n-heptane. Thus, a free-standing subchronic NOAEL of 3,000 ppm n-pentane for neurotoxicity was identified from this study. The NOAEL is consistent with that identified from the Frontalli et al. (1981) study. However, since this NOAEL was based on a 16-week subchronic study, it was not used as the POD. The TD used the NOAEL of 3,000 ppm based on the 30-week chronic study by Frontalli et al. (1981) as the POD to derive chronic toxicity values although both NOAELs were similar.

4.1.4.3 McKee et al. (1998) Study

McKee et al. (1998) reported a subchronic inhalation toxicity study which was carried out in the EBS Toxicology Laboratory in 1997. Groups of 20 CrI:CDBR SD rats (ten males and ten females) were exposed 6 h/d, 5 d/week for 13 weeks to n-pentane 0 (control), 5,000, 10,000, and 20,000 mg/m³. The mean actual chamber concentrations for the exposed groups were 5,097 ± 79, 10,203 ± 151 and 20,483 ± 734 mg/m³, respectively. Necropsy, hematology, and serum chemistry studies were performed on all animals and selected tissues and organs were weighed and preserved at study termination. All tissues from the high and control groups, and respiratory tract tissue and all gross lesions from the mid and low exposure groups were examined. No signs of systemic toxicity were observed during the study or at study termination. There were no adverse effects with respect to clinical signs, body weight changes, food consumption, clinical pathology parameters, organ weights, post-mortem observations, or microscopic changes. This study was conducted in accordance with GLP conditions. A free-standing NOAEL of approximately 20,000 mg/m³ (6,800 ppm) was identified from this study. While the TD noticed that a larger number of animals/group and multiple exposure groups were performed in the McKee et al. (1998) study, the NOAEL identified from this study was based on a 13-week subchronic study; it was not used as the POD.

4.1.5 Reproductive/Developmental Toxicity Studies

Pentane is considered of no concern due to reproductive/developmental effects, although reproductive/developmental studies were only conducted in one species, the rat. Although one- or two-generation reproductive toxicity studies with pentane were not available, in the 13-week oral subchronic inhalation EBS study (see Section 4.1.4.3 McKee et al. 1998 Study), no signs of toxicity were observed on the reproductive system by macroscopic or microscopic evaluation after exposure to n-pentane up to 20,000 mg/m³ (6,800 ppm).

4.1.6 MOA Analysis and Dose Metric

As indicated in Section 3.3, inhaled n-pentane is absorbed by the lungs and rapidly eliminated by exhalation or metabolism. Only a minor part of the dose is excreted as metabolites in urine since the initially formed products are rapidly converted by a cytochrome p450-dependent oxidation (2- and 3-pentanol) to CO₂. The half-life is approximately 0.13 h (EU 2003). Because of the rapid metabolism and excretion of n-pentane, potential for repeated dose toxicity is expected to

be low (McKee et al. 1998, Galvin and Marashi 1999, Lammers et al. 2011). Data on the exposure concentration of the parent chemical are available, whereas data on more specific dose metrics are not available. Thus, exposure concentration of the parent chemical will be used as the default dose metric.

4.1.7 POD for the Key Study and Critical Effect

The chronic free-standing NOAEL of 3,000 ppm for neurotoxicity identified from the Frontalli et al. (1981) study were used as the POD for deriving the chronic ReV since it was the only chronic exposure study (see Section 4.1.3 and 4.1.4). The critical effects noted in rats are considered relevant to humans.

4.1.8 Dosimetric Adjustments

4.1.8.1 Exposure Duration Adjustments

According to Section 4.3.2 of the ESL Guidelines (TCEQ 2006), the chronic POD of 3,000 ppm was then adjusted from discontinuous exposure (9 h/d, 5 d/week) to continuous exposure concentration using the following dosimetric adjustments:

$$\begin{aligned} \text{POD}_{\text{ADJ}} &= \text{POD} \times D/24 \times F/7 \\ \text{POD}_{\text{ADJ}} &= 3,000 \text{ ppm} \times 9/24 \times 5/7 \\ \text{POD}_{\text{ADJ}} &= 803.57 \text{ ppm} \end{aligned}$$

where:

$$\begin{aligned} \text{POD}_{\text{ADJ}} &= \text{POD from an animal study, adjusted to a continuous exposure duration} \\ \text{POD} &= \text{POD from an animal study, based on a discontinuous exposure duration} \\ D &= \text{exposure duration, h/d} \\ F &= \text{exposure frequency, d/week} \end{aligned}$$

The POD_{ADJ} of 803.57 was then used to conduct the default dosimetric adjustment to a POD_{HEC} .

4.1.8.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Chronic exposure to n-pentane causes neurotoxic effects which are systemic rather than POE effects. As indicated in Section 3.5.2, n-pentane was considered a Category 3 gas and a default value of 1 was used for the $(\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}}$ ratio. The resulting POD_{HEC} from the POD_{ADJ} of 803.57 ppm in the Frontalli et al. (1981) study is 803.57 ppm.

4.1.9 Adjustments of the POD_{HEC}

The POD_{HEC} of 803.57 ppm was used to set the chronic ReV and $\text{chronicESL}_{\text{nonlinear(nc)}}$. The following UFs were applied to the POD_{HEC} :

- a UF_{H} of 10 for intraspecies variability,

- a UF_A of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences, and
- a UF_D of 3 was used because only one species was used to evaluate toxicity, including reproductive/developmental effects and none of the animal studies showed dose-response relationships in inhalation bioassays. Confidence is considered medium on the database
- A UF_{sub} of 1 was used because the Frontalli et al. (1981 study was conducted for 30 weeks, considered to be a chronic study since it is more than 10% of the lifetime of the rat
- The total $UF = 100$.

$$\begin{aligned}\text{Chronic ReV} &= \text{POD}_{\text{HEC}} / (UF_H \times UF_A \times UF_D \times UF_{\text{sub}}) \\ &= 803.57 \text{ ppm} / (10 \times 3 \times 3 \times 1) \\ &= 8.0357 \text{ ppm} \\ &= 8,000 \text{ ppb (rounded to two significant figures)}\end{aligned}$$

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

Accordingly, by applying a total UF of 100 to the POD_{HEC} of 803.57 ppm, the chronic ReV is 8,000 ppb (24,000 $\mu\text{g}/\text{m}^3$). The $^{chronic}ESL_{\text{nonlinear(nc)}}$ of 2,400 ppb (7,100 $\mu\text{g}/\text{m}^3$) was set according to the ESL guidance (TCEQ 2006) based on the chronic ReV multiplied by a HQ of 0.3 (Table 6).

Table 6. Derivation of the Chronic ReV and ^{chronic}ESL_{nonlinear(nc)}

Study	Frontalli et al. 1981
Study Population	SD rats
Study Quality	Medium
Exposure Method	Inhalation exposure of rats to 0, or 3,000 ppm n-pentane vapor
Critical Effects	Free-standing NOAEL
POD	3,000 ppm (free-standing NOAEL)
Exposure Duration	9 h/day, 5 d/week for 30 weeks
Extrapolation to continuous exposure (POD _{ADJ})	803.57 ppm
POD _{HEC}	803.57 ppm (NOAEL _{HEC})
Total UFs	100
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL-to-NOAEL UF</i>	Not applicable
<i>Subchronic to chronic UF</i>	1
<i>Incomplete Database UF</i>	3
<i>Data Quality</i>	Medium
Chronic ReV (HQ = 1)	24,000 µg/m³ (8,000 ppb)
^{chronic}ESL_{nonlinear(nc)} (HQ = 0.3)	7,100 µg/m³ (2,400 ppb)

4.2 Carcinogenic Potential

No information on the genotoxic potential of pentane in humans is available. n-Pentane was negative on mutagenicity in two reverse mutation assays in *Salmonella typhimurium* (Kirwin et al. 1908 and Epstein et al. 1972, as cited in Galvin 1999a). No biologically significant increases in chromosomal aberrations were observed in CHO cells. In a 90-d subchronic inhalation toxicity study by McKee et al. (1998) and EBS (1997, as cited in EU 2003), n-pentane did not induce any increase in micronuclei formation and did not induce bone marrow cytotoxicity in rats at doses up to 20,000 mg/m³ (6,800 ppm). The authors suggested that carcinogenic potential of pentane exposure is highly unlikely. No data were found on long-term toxicity or carcinogenicity studies on pentane (Galvin and Marashi 1999, Galvin and Panson 1999; EU 2003). Because there are no available data to assess carcinogenicity in humans or animals, the ^{chronic}ESL_{linear(c)} was not developed (EU 2003). According to the Guidelines for Carcinogen Risk Assessment (USEPA, 2005), the database for pentane provides "inadequate information to assess carcinogenic potential."

4.3 Welfare-Based Chronic ESL

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

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

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

- chronic ReV = 24,000 µg/m³ (8,000 ppb)
- ^{chronic}ESL_{nonlinear(nc)} = 7,100 µg/m³ (2,400 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 24,000 µg/m³ (8,000 ppb) is used (Table 1).

The long-term ESL for air permit evaluations is the ^{chronic}ESL_{nonlinear(nc)} of 7,100 µg/m³ (2,400 ppb) (Table 2). The ^{chronic}ESL_{nonlinear(nc)} (HQ = 0.3) is not used for evaluation of air monitoring data.

Chapter 5 References

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