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n-Butane and Isobutane

CAS Registry Number:

n-Butane: 106-97-8

Isobutane: 75-28-5

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on July 31, 2012.

Revised DSD September 14, 2015:

(1) the odor-based value was withdrawn because n-butane does not have a pungent, disagreeable odor (TCEQ 2015a).

(2) the chronic ReV was updated to use the chronic ReV of n-pentane as directed in the updated TCEQ guidelines (2015b)

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	acute exposure guideline level
AMCV	air monitoring comparison value
^{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
$^{acute}ESL_{odor}$	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
$^{chronic}ESL_{linear(c)}$	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
EU	European Union
FOB	functional observational battery
GC	gas chromatography
GD	gestation day
GLP	good laboratory practice
GRAS	generally recognized as safe

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
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
LEL	lower explosive limit
LOAEL	lowest-observed-adverse-effect-level
LPG	liquefied petroleum gas
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number
NAC	National Advisory Committee
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration
POD	point of departure

Acronyms and Abbreviations	Definition
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
RGDR	regional gas dose ratio
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

Chapter 1 Summary Tables and Figure

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of two isomers of butane (n-butane and isobutane). Please refer to Section 1.6.2 of theTCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), 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 n-butane and isobutane's physical/chemical data. Figure 1 compares the values in Tables 1 and 2 to values developed by other federal/occupational organizations.

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

Short-Term Values	Concentration	Notes
acute ReV **for n-butane**	220,000 µg/m^3 (92,000 ppb) **for n-butane**	**Critical Effect:** Free-standing NOAEL due to lack of general systemic effects observed in rats in key study
acute ReV **for isobutane**	78,000 µg/m^3 (33,000 ppb) **for isobutane**	**Critical Effect:** Free-standing NOAEL due to lack of cardiac and pulmonary response observed in human volunteers in key study
$^{acute}ESL_{odor}$	---	Natural gas or petroleum-like odor
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	24,000 µg/m^3 (10,000 ppb) **Long-Term Health**	The minimum database for development of a chronic ReV was not met. The pentane chronic ReV is used as a surrogate
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[*] Based on the chronic ReV of 24,000 µg/m^3 for pentane (see Section 4.2).

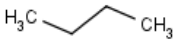
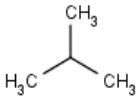
Table 2. Air Permitting Effects Screening Levels (ESLs)

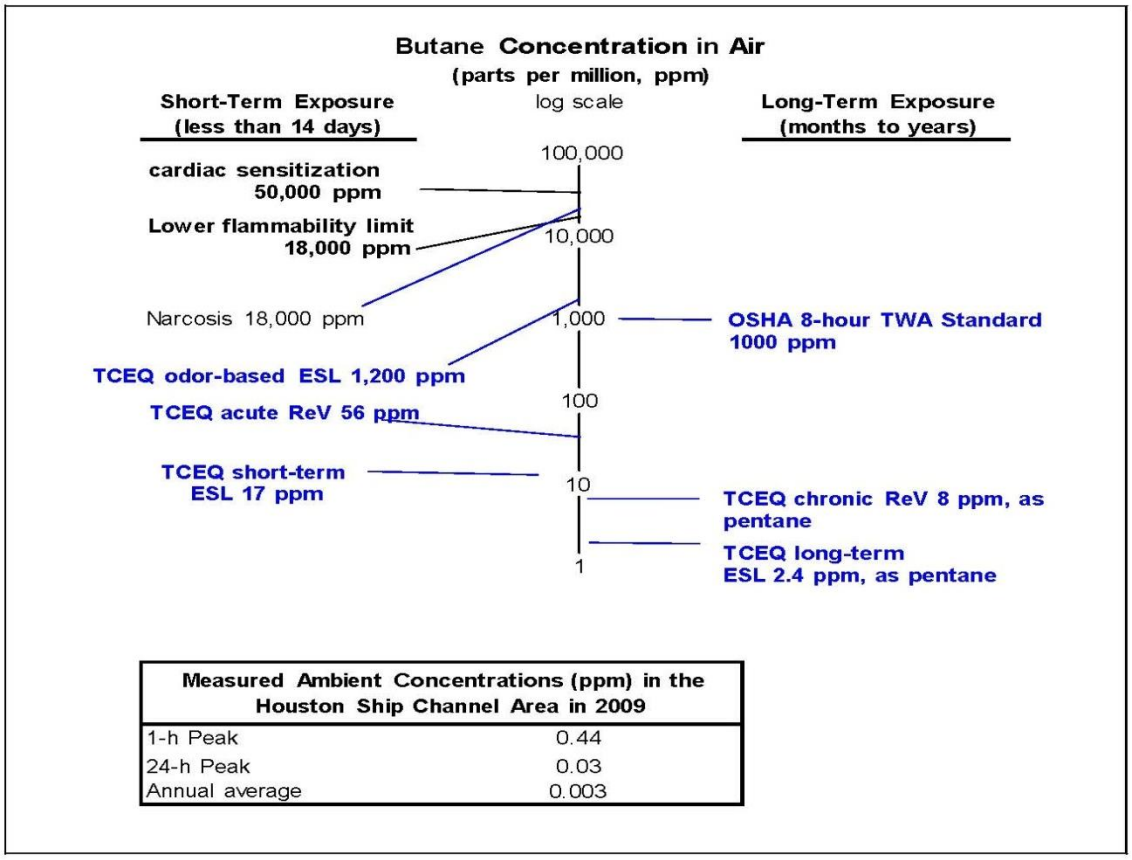
Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3) for n-butane	66,000 µg/m^3 (28,000 ppb)[a] for n-butane **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Free-standing NOAEL due to lack of general systemic effects observed in rats in key study
^{acute}ESL [1 h] (HQ = 0.3) for isobutane	23,000 µg/m^3 (10,000 ppb)[a] for isobutane **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Free-standing NOAEL due to lack of cardiac and pulmonary response observed in human volunteers in key study
^{acute}ESL$_{odor}$	---	Natural gas or petroleum-like odor
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	7,100 µg/m^3 (3,000 ppb)[b] **as pentane** **Long-Term ESL for Air Permit Reviews**	The minimum database for development of a chronic ESL was not met. The pentane chronic ESL is used as a surrogate
^{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 160,000 µg/m^3 (6,700 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ESL of 7,100 µg/m^3 for pentane (see Section 4.2)

Table 3. Chemical and Physical Data

Parameter	n-Butane	Isobutane	Reference
Chemical Structure			ChemIDPlus
Molecular Weight	58.12	58.12	ACGIH (2001)
Molecular Formula	C_4H_{10}	C_4H_{10}	ACGIH (2001)
Structural Formula	CH_3-CH_2- CH_2- CH_3	$(CH_3)_2$-CH- CH_3	ACGIH (2001)
Physical State	Gas	Gas	ACGIH (2001)
Color	Colorless	Colorless	ACGIH (2001)
Odor	Slight, natural gas	Slight, natural gas	ACGIH (2001)
CAS Registry Number	106-97-8	75-28-5	ACGIH (2001)
Synonyms/Trade Names	Butyl hydride; Diethyl; Methylethyl methane	1,1-Dimethylethane; 2-Methylpropane; Triethylmethane	ACGIH (2001)
Solubility in water @25°C	Practically insoluble (61.2 mg/L)	Practically insoluble (48.8 mg/L)	ChemIDPlus
Log K_{ow}	2.89	2.76	ChemIDPlus
Vapor Pressure @25°C	1820 mm Hg	2610 mm Hg	ChemIDPlus
Vapor Density (air = 1)	2.07 @0°C	2.07 @0°C	ACGIH (2001)
Density (water = 1)	0.5788 @ 20°C	0.5571 @ 20°C	ACGIH (2001)
Melting Point	- 1.38E+02°C	- 1.38E+02°C	ChemIDPlus
Boiling Point	- 0.5°C	- 11.7°C	ChemIDPlus
Lower Explosive Limit (LEL)	1.86%	1.8%	ACGIH (2005)
Conversion Factors	1 ppm = 2.37 mg/m^3 1 mg/m^3 = 0.42 ppm	1 ppm = 2.37 mg/m^3 1 mg/m^3 = 0.42 ppm	Toxicology Staff



Measured Ambient Concentrations (ppm) in the Houston Ship Channel Area in 2009	
1-h Peak	0.44
24-h Peak	0.03
Annual average	0.003

Figure 1 Butane Health Effects and Regulatory Levels

Figure 1 compares butane's acute toxicity values (acute ReV, odor-based ESL, and health-based, short-term ESL) and chronic toxicity values (generic chronic ReV and long-term ESL) found in Table 1 and 2 to highest measured ambient concentrations in Houston, Texas in 2009 and the Occupational Safety and Health Administration (OSHA) occupational exposure values.

Chapter 2 Major Sources or Uses and Ambient Air Concentrations

General butane (hereafter, butane) is a colorless, flammable gas with a petroleum-like odor. Butane consists of two isomers: n-butane and isobutane. They are derived from natural gas and petroleum and are inert to most chemical reagents. Both isomers of butane are low molecular weight alkanes and generally used as refrigerants, for gas lighter refills, aerosol propellants, instrument calibration fluids, fuel sources, and Generally Recognized as Safe (GRAS) food ingredients (Moore 1982, ACGIH 2001, Galvin and Bond 1999). n-Butane is used in the production of ethylene and 1,3-butadiene, as a chemical feedstock for special chemicals in the solvent, rubber, and plastics industries, in the blending of gasoline or motor fuel, as a constituent in liquefied petroleum gas (LPG), and as an extraction solvent in deasphalting processes (Low et al. 1987, as cited in AEGL 2008). Isobutane is used as a raw material for petrochemicals and an industrial carrier gas. Isobutane is also a raw material in the chemical industry for the production

of propylene glycols and oxides and polyurethane foams and resins (Moore 1982, ACGIH 2001, Galvin and Bond 1999).

Butane can be released into the air from its production and use in many products associated with the petroleum and natural gas industries. In addition, the combustion of gasoline is a major mechanism for the release of butane into the atmosphere. Waste incinerators, hazardous waste disposal sites, and landfills also release butane into the environment (HSDB 2010). According to the National Ambient Volatile Organic Compounds Database, the median rural, suburban, and urban atmospheric concentrations of n-butane are 0.78, 8.8, and 9.2 ppb, respectively. The median concentrations of isobutane in remote, rural, suburban, and urban area are 0.158, 0.340, 3.8, and 3.3 ppb, respectively (Shah et al. 1988, as cited in HSDB 2010). Concentrations of n-butane measured at the Jones State Forest in rural Texas ranged from 12.0 to 49.6 ppb with an average of 24.1 ppb for 10 samples (Saila 1979, as cited in HSDB 2010). In 2009, a Houston Ship Channel ambient air monitoring site (Milby Park) that collects both 1-h and 24-h n-butane highest reported concentrations (Auto GC) of 442 and 29 ppb, respectively. The 1-h and 24-h isobutane highest reported concentrations (Auto GC) were 1,319 and 78 ppb, respectively. The annual average concentration for n-butane and isobutane were 3.3 and 2.1 ppb, respectively.

Chapter 3 Acute Evaluation

3.1 Physical/Chemical Properties

Butane is a colorless and flammable gas with a natural gas odor. It exists in two isomeric forms: n-butane and isobutane (ACGIH 2001, 2005). The main chemical and physical properties of these two isomers are summarized in Table 3.

3.2 Health-Based Acute ReV and ESL

Butane is a low molecular weight aliphatic hydrocarbon which is an anesthetic and asphyxiant. It is essentially non-toxic at low concentrations and has a low acute respiratory toxicity to experimental animals and humans at moderate concentrations. Inhalation of extremely high concentrations exceeding butane's lower explosive limit (LEL: 1.8-1.9%) may cause effects and depression of the central nervous system (CNS) with symptoms such as headache, nausea, dizziness, drowsiness, confusion, and unconsciousness (Moore 1982, Berzins 1994, Galvin and Bond 1999). 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 in effects such as lethality, anaesthetic 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). Futhermore, 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 to approximately 2 hours (e.g., n-decane) (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). Similar results were reported by Stoughton and Lamson (1936) that isobutane was less anesthetic and lethal than n-butane. Stoughton and Lamson (1936) also concluded that butane was less anesthetic and lethal than pentane. One reason why isobutane could be less active than n-butane is that branched hydrocarbons are less well absorbed than less branched or unbranched isomers (Dahl et al. 1988, Galvin and Bond 1999).

Stoughton et al. (1936) reported that light anesthetic effects (inability to maintain an upright position) were observed in mice exposed to 13% (130,000 ppm) for 25 min or 22% (220,000 ppm) of n-butane in air for 1 min. Exposure to 27% (270,000 ppm) of n-butane for 2 hours (h) caused death in 60% of mice (average time of death 84 min). Isobutane was less active in anesthetic effects and less lethal than n-butane. Inhaled isobutane caused light anesthetic effects in mice exposed to 15% (150,000 ppm) for 60 min and 23% (230,000 ppm) concentrations for 26 min, and exposure to 41% (410,000 ppm) for 2 h caused death in 60% of mice (average time of death 72 min). The safety margin between anesthetic and lethal concentrations appears to be very narrow.

Butane is also a weak cardiac sensitizer in humans following inhalation exposures to high concentrations. Exposure to 5% (50,000 ppm) of isobutane for 5 min may also cause cardiac sensitization resulting in irregular heartbeat and may make the individual more susceptible to cardiac effects of substances such as epinephrine and adrenaline (Reinhardt et al. 1971). Cardiac sensitizers may cause the sudden onset of an irregular heartbeat (cardiac arrhythmia) and, in some cases, sudden death. Sudden deaths have been reported in cases of substance abuse involving butane (Rohrig 1997, Fuke et al. 2002). Although case reports indicate that butane may cause arrhythmias in humans exposed to high concentrations of butane, no adequate human or animal data are available to evaluate this endpoint in a quantitative way. The case reports do not provide adequate data for the derivation of toxicity values.

3.2.1 Key Studies

Information from human studies regarding the acute toxicity of butane is limited. Exposure to low concentrations of butane has not been reported to cause adverse effects in humans. No exposure-related effects were noted in human volunteers after exposure to isobutane at 250 to 1,000 ppm (Stewart et al. 1977). Humans exposed to butane at 10,000 ppm for 10 min resulted in drowsiness, but no other evidence of systemic effects was present (Patty and Yant 1929). Animal data indicate that acute butane exposures at concentrations above its lower explosive limit (LEL) (1.8% or 18,000 ppm) can elicit anesthesia, CNS depression, and cardiac arrhythmia. 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).

Two human studies (Patty and Yant 1929, Stewart et al. 1977) and animal studies (Halder et al. 1986, Reinhardt et al. 1971, Hoffman 2008 and 2010) that investigated butane provide useful information on toxicity. For reasons discussed below, the Hoffman (2008) animal 2-week subacute inhalation study was chosen as the key study to develop the acute ReV and ESL for n-butane, while the Stewart et al. (1977) human acute inhalation study was chosen as the key study to develop the acute ReV and ESL for isobutane. All studies were conducted in multiple exposure levels.

3.2.1.1 n-Butane Key Study (Hoffman 2008)

In a preliminary range-finding study for a 4-week subacute study conducted by Huntington Life Sciences (HLS) (Hoffman 2008), male and female Sprague-Dawley (SD) CD rats (10/sex/group) were exposed via whole-body inhalation to 0, 90, 900 or 9,000 ppm (target concentrations) n-butane for 6 h/day (d), 7 d/week for two weeks. The mean (± standard deviation) analytical exposure concentrations were determined to be 0 ± 0, 91.26 ± 4.74, 910.5 ± 32.9 and 9,197 ± 328 ppm for the control and the respective exposure groups. Viability, clinical observations, body weights, food consumption, organ weights and macroscopic observations were evaluated. This study was conducted in compliance with USEPA and Organization for Economic Cooperation and Development (OECD) Good Laboratory Practices (GLP) (Hoffman 2008). All animals survived to termination. There were no statistically significant differences in body weights, organ weights or in feed consumption in animals at all exposure levels compared to control animals. No gross abnormalities related to n-butane exposure were evident at necropsy examination. Thus, the free-standing NOAEL for general systemic effects was 9,197 ppm (mean analytical concentration) and was used as the point of departure (POD) to derive the acute ReV and ^{acute}ESL for n-butane.

3.2.1.2 Isobutane Key Study (Stewart et al. 1977)

In an acute and repetitive inhalation study by Stewart et al. (1977), eight healthy adult male and female volunteers were exposed to isobutane in a controlled-environment chamber to a series of gas concentrations ranging from 250 to 1000 ppm. The eight human subjects were first exposed to a series of single exposure to 250, 500, and 1,000 ppm for 1 min, 2 min, 10 min, 1 h, 2 h, or 8 h. The eight volunteers were then exposed repeatedly to isobutane at concentrations of 500 ppm for 1, 2, or 8 h/d, 5 d/week, for 2 weeks. Serial clinical testing emphasizing on evaluating the cardiac and pulmonary response to these exposures was conducted. Additionally, spontaneous electroencephalograms (EEG) and visual evoked response (VER) were recorded four times a day, 3 d/week of the 2-week period of exposure.

The results showed that acute exposures to isobutane in concentrations of 250, 500, or 1,000 ppm did not produce any measurable physiological effect in pulmonary function, cardiac function, neurological responses, subjective response, adrenocortical function, or cognitive response even though isobutane was readily detectable in the breath and blood in any human subjects. A free-standing NOAEL of 1,000 ppm for acute exposures to isobutane up to 8 h was identified from the first experiment. Repeated exposures to isobutane 500 ppm up to 2 weeks were also without

any measurable untoward physiological effect. However, there was a significant reduction in the VER wave amplitude recorded during the second week of repetitive exposure to isobutane at 500 ppm. The authors indicated that this type of reduction can be due to CNS depression and has been observed prior to the development of overt signs of neurological impairment. The level of 500 ppm can be considered a free-standing LOAEL for the 2-week repetitive exposure. The free-standing NOAEL of 1,000 ppm for acute exposure was used as the POD to derive the acute ReV and ^{acute}ESL for isobutane.

3.2.2 Supporting Studies for n-Butane and Isobutane

3.2.2.1 n-Butane (Hoffman 2010)

In a four-week subacute toxicity study conducted by HLS (Hoffman 2010), male and female SD CD rats (12/sex/group) were exposed via whole-body inhalation to 0, 900, 3,000 and 9,000 ppm (target concentrations) n-butane gas for 6 h/d, 7 d/week for four weeks. The mean (± standard deviation) analytical exposure concentrations were determined to be 0 ± 0, 930.6 ± 28.1, 3,022 ± 58 and 9,157 ± 269 ppm for the control and the respective exposure groups. Viability, clinical observations, body weights, food consumption, functional observational battery (FOB) and motor activity were evaluated. Clinical and microscopic pathology was conducted on rats in the control and high exposure groups. All animal survived to termination. There were no statistically significant differences in body weights, organ weights or in feed consumption in animals at all exposure levels compared to the control animals. There were no apparent exposure-related differences in FOB or motor activity parameters, or in clinical chemistry levels. No gross abnormalities related to n-butane exposure were evident at microscopic examination. A NOAEL of 9,000 ppm for general systemic effects was identified from this 4-week subacute exposure study. Since the NOAEL is the same as that identified from a 2-week subacute exposure key study (Hoffman 2008), it was not used as the POD to derive the acute ReV and ^{acute}ESL for n-butane.

3.2.2.2 n-Butane (Patty and Yant 1929)

In a human inhalation study, no symptoms except drowsiness were experienced by three to six volunteers exposed to up to 10,000 ppm butane for 10 min (Patty and Yant 1929). The drowsiness reported in volunteers in this study, however, was not explicit. It was only stated in a table that exposure to 10,000 ppm for 10 min produced drowsiness in volunteers. However, it was stated in the text that no symptoms were noted. AEGL (2008) indicated that several alkanes (C_3 to C_7) were studied in this experiment and more severe effects were mentioned for hexane and heptane suggesting that if effects were observed with butane they would have been described more explicitly. It was concluded that the drowsiness reported apparently was of a very minor severity (AEGL 2008). Thus, the level of 10,000 ppm was considered a free-standing NOAEL. This study is rather dated and focused on a limited number of parameters to examine the warning properties of butane. The physiological response reported by the tested subjects during the odor intensity tests was subjective and the number of tested subjects was small. This study is rather dated and focused on a limited number of parameters to examine the warning properties of

butane, evaluated only 3-6 subjects, study results were not well reported, and exposure was for only 10 min. Further, the free-standing NOAEL of 10,000 ppm is slightly higher than that identified from the Hoffman 2008 key study. Thus, the NOAEL of 10,000 ppm identified from this study was not used as the POD to derive the acute ReV and ^{acute}ESL for n-butane.

3.2.2.3 n-Butane (Nuckolls 1933, as cited in AEGL 2008)

In a limited historical study by Nuckolls (1933, as cited in AEGL 2008), guinea pigs (3/group) were exposed to 2.1-2.8% (21,000-28,000 ppm) or 5.0-5.6% (50,000-56,000 ppm) of n-butane for 5 min, 30 min, 1 h or 2 h. The animals appeared normal with exposure to 2.1-2.8% for 5 min. Somewhat irregular breathing was noted with exposure to 2.1-2.8% for 30 min, 1 h or 2 h. With exposure to 5.0-5.6%, no significant effects were observed in animals exposed for 5 min. With exposure for 30 min, 1 h or 2 h, the animals showed occasional retching, irregular breathing, appeared dazed, and/or responded slowly to sound. All animals recovered quickly and appeared normal during a 10-d observation period. Autopsy of one animal exposed to 5.0-5.6% for 2 h showed no effects. A free-standing LOAEL of 21,000 ppm for 30 min, 1 h or 2 h exposure for minor irregular breathing was identified from this study. The LOAEL value of 2.1-2.8% was high and a NOAEL was not identified and thus, was not used as the POD to develop the acute ReV and $_{acute}$ESL for n-butane.3.2.2.4 Isobutane (Reinhardt et al. 1971)

In an aerosol “sniffing” study by Reinhardt et al. (1971), Groups of 6-12 healthy, male beagle dogs (13-26 months old) were exposed to isobutane at 2.5, 5, or 10-20% (25,000, 50,000, or 100,000-200,000 ppm, nominal concentrations) for a duration of five min. This was followed by administration of a challenge injection of epinephrine and the recording of an electrocardiogram (ECG) to determine the effect of this procedure on the cardiac rhythm. A” marked response” was recorded when an arrhythmia developed which was considered to represent a significant cardiac sensitization effect or which ended in cardiac arrest (ventricular fibrillation). The ECG results showed that marked response was not recorded in any of 12 tested dogs exposed to 2.5% isobutane. However, marked responses were recorded in four of 12 dogs exposed to 5% with one case of cardiac arrest included in marked response, and were recorded in all six dogs exposed to 10-20% isobutane with three cases of cardiac arrest included in marked response. A NOAEL of 25,000 ppm (2.5%) and a LOAEL of 50,000 ppm (5%) for cardiac arrhythmia were identified from this study. The NOAEL of 25,000 ppm is much higher than that identified from the Stewart et al. (1977) human study and thus, was not used as the POD to develop the acute ReV and ^{acute}ESL for isobutane.

3.2.2.4 Isobutane (Reinhardt et al. 1971)

In an aerosol “sniffing” study by Reinhardt et al. (1971), Groups of 6-12 healthy, male beagle dogs (13-26 months old) were exposed to isobutane at 2.5, 5, or 10-20% (25,000, 50,000, or 100,000-200,000 ppm, nominal concentrations) for a duration of five min. This was followed by administration of a challenge injection of epinephrine and the recording of an electrocardiogram (ECG) to determine the effect of this procedure on the cardiac rhythm. A” marked response” was recorded when an arrhythmia developed which was considered to represent a significant cardiac

sensitization effect or which ended in cardiac arrest (ventricular fibrillation). The ECG results showed that marked response was not recorded in any of 12 tested dogs exposed to 2.5% isobutane. However, marked responses were recorded in four of 12 dogs exposed to 5% with one case of cardiac arrest included in marked response, and were recorded in all six dogs exposed to 10-20% isobutane with three cases of cardiac arrest included in marked response. A NOAEL of 25,000 ppm (2.5%) and a LOAEL of 50,000 ppm (5%) for cardiac arrhythmia were identified from this study. The NOAEL of 25,000 ppm is much higher than that identified from the Stewart et al. (1977) human study and thus, was not used as the POD to develop the acute ReV and ^{acute}ESL for isobutane.

3.2.2.5 Mixture of C_4/C_5 hydrocarbons (Halder et al. 1986)

Halder et al. (1986) conducted a three-week inhalation study to evaluate the nephrotoxicity of a mixture of C_4/C_5 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/m^3 (44 ppm), 1,150 mg/m^3 (432 ppm) or 11,800 mg/m^3 (4,437 ppm) (time-weighted average analytical concentrations) C_4/C_5 hydrocarbon mixture for 6 h/d, 5 d/week for three 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 C_4/C_5 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/m^3 (4,437 ppm). The level is considered a NOAEL for the mixture of C_4/C_5 hydrocarbons. However, since the exposure was a mixture of C_4/C_5 hydrocarbons and the main endpoint evaluated (male rat hydrocarbon-induced nephropathy) is irrelevant to humans, it was not appropriate to use as the POD to develop toxicity values for butane.

3.2.3 Reproductive/Developmental Toxicity Studies

Reproductive/developmental toxicity was also studied in the Hoffman (2010) study (see Section 3.2.2.1), additional female SD CD rats (12/group) were exposed to 0, 900, 3,000 and 9,000 ppm (nominal concentrations) n-butane gas for 6 h/d, 7 d/week for at least two weeks prior to mating initiation and continued to be treated, 6 h/d, during mating. Once mated, female rats were treated, 6 h/d, during gestation days (GD) 0-19. All mated female rats were found pregnant and delivered live pups. There were no treatment-related differences in mating, fertility and gestation indices, other reproductive parameters up to the time of parturition, and all parturition parameters, when compared to the control group. There were also no exposure-related differences in body weights or weight gains, and macroscopic postmortem evaluations in the pups feeding from exposed animals compared to the pups feeding from control animals. No adverse effects on reproductive performance and no effects on pup survival and developmental to postnatal day 4. A free-standing NOAEL of 9,000 ppm for reproductive/developmental and neonatal effects was identified from this study. Since the NOAEL is the same as that identified from a 2-week

subacute exposure key study (Hoffman 2008) and provides no additional potential critical effect (CNS), it was not used as the POD to derive the acute ReV and ^{acute}ESL for n-butane.

3.3 Mode of Action (MOA) Analysis and Dose Metric

Inhaled n-butane or isobutane are absorbed by the lungs and largely excreted unchanged in exhaled air and metabolism represents a minor route of elimination. Gill et al. (1991, as cited in AEGL 2008) reported that four human subjects (3 males, 1 female, 20-21-years of age) were exposed to 600 ppm n-butane for 4 h. The pulmonary uptake appears to increase very fast within the first 5 min of exposure and reaches a plateau within the first 30 min of exposure. Pulmonary uptake remained fairly constant for the individual subjects during the remainder of the exposure and ranged from approximately 30 to 50% between the four subjects. n-Butane concentration in exhaled breath and in blood decreased rapidly to less than 5 ppm and 0.02 µg/ml, respectively, 20 min postexposure. Wagner (1974, as cited in Galvin and Bond 1999) reported 14% isobutane was absorbed in volunteer subjects inhaling 100 ppm isobutane for 20 min. API (1987, as cited in Galvin and Bond 1999) reported the uptake for isobutane was 5.4% in male F344 rats exposed to 1,000-5,000 ppm isobutane vapor for 80 to 100 min.

Aliphatic hydroxylation is the major metabolic pathway which occurs in rat liver microsomes to produce 2-butanol and methyl ethyl ketone (MEK) from n-butane, and tert-butanol from isobutane as the respective metabolites. Tsukamoto et al. (1985) exposed male ICR mice for 1 h to a mixture of n-butane, air, and oxygen (in the proportion of 2:1:1, thus 500,000 ppm n-butane). MEK and sec-butanol were detected in blood and tissues as metabolites. Tissue concentrations of MEK ranged from 2.9 to 4 µg/g with the highest levels in blood, followed by liver, kidney, and brain. The sec-butanol concentration in these tissues ranged from 30 to 35 µg/g, with the highest levels in blood, followed by brain. Shugaev (1969) reported that inhaled butane is partially absorbed in the rat lung and is translocated to the brain, kidney, liver, spleen, and perinephric fat. The brain levels of butane were found correlated with the degree of CNS depression and narcosis in both mice and rats. Because of its volatile nature, elimination of butane by exhalation can be anticipated. Its elimination half-life is 0.13 h at nonsaturating concentrations (Low et al. 1987, as cited in Carreón T. 2005).

Animal data indicate that acute butane exposures at concentrations above its LEL can elicit anesthesia, CNS depression, and cardiac arrhythmia. The MOAs for these effects have not been fully elucidated. Therefore, as a default, a threshold, nonlinear dose-response relationship is used. 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

For n-butane, the two-week subacute NOAEL of 9,197 ppm for general systemic effects identified by Hoffman (2008) was used as the POD to derive the acute ReV and ^{acute}ESL for n-butane. For isobutane, the acute NOAEL of 1,000 ppm for systemic effects, and the 2-week

subacute LOAEL of 500 ppm for CNS depression identified by Stewart et al. (1977) for supporting values, was used as the POD to derive the acute ReV and ^{acute}ESL for isobutane.

3.5 Dosimetric Adjustments

3.5.1 Exposure Duration Adjustments

3.5.1.1 n-Butane

Like pentanes, the results from both the 2-week and 4-week subacute key studies (Hoffman 2008, 2010) showed that that concentration is the dominant determinant of toxicity (see Section 3.2.1.1 and 3.2.2.1). Additionally, the MOA information for butane has not been fully elucidated and the elimination half-life is short. Therefore, the TD assumes there is no change in concentration (TECQ 2006). The POD of 9,197 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).

3.5.1.2 Isobutane

Since the exposure duration for the NOAEL of 1,000 ppm identified from the Stewart et al. (1977) study included 1-h exposure, there is no adjustment from an exposure duration to 1-h. Thus, the POD was directly used as a POD_{HEC} to set the acute ReV and ^{acute}ESL.

3.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure (Hoffman 2008)

Butane is practically water insoluble. Acute exposures to butane cause general systemic rather than point-of-entry (POE) effects. In addition, toxicokinetic data on butane indicate that butane is rapidly absorbed via the lungs and widely distributed within the body. Butane was therefore considered a Category 3 gas (USEPA 1994, as cited in TCEQ 2006). For Category 3 gases, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

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

The measured blood/air partition coefficient in human ($(H_{b/g})_H$) for n-butane is 0.18. No measured blood/air partition coefficient in the rat ($(H_{b/g})_A$ is available; however, a predicted $(H_{b/g})_A$ of 0.2925 was reported by Meulenberg and Vijverberg (2000). Because the ratio of the animal-to-human partition coefficients (0.2925/0.18 = 1.63) is greater than one, a default value of one (1) is used as the regional gas dose ratio (RGDR) (i.e., $(H_{b/g})_A/(H_{b/g})_H$) as recommended by the TCEQ ESL guidelines (2006). The resulting POD_{HEC} from the POD of 9,197 ppm in the Hoffman (2008) rat study is 9,197 ppm for n-butane.

3.5.3 Adjustments of the POD_{HEC}

3.5.3.1 n-Butane

For the POD_{HEC} of 9,197 ppm for the Hoffman (2008):

The POD_{HEC} of 9,197 ppm obtained from the default dosimetric adjustment for Category 3 gases was used to derive the acute ReV and ^{acute}ESL for n-butane. 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 for uncertainty associated with an incomplete database because animal studies were conducted for different toxicity endpoints including reproductive/developmental effects, and multiple animal species were used in inhalation bioassays. However, human studies for pure n-butane were limited. Confidence is considered medium on the database because none of animal studies showed dose-response relationships in inhalation bioassays. The quality of the key rat study, however, is high.
- The total UF = 100.

Acute ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 9,197 ppm / (10 x 3 x 3)
= 91.97 ppm
= 92,000 ppb (rounded to two significant figures)

3.5.3.2 Isobutane

The POD_{HEC} of 1,000 ppm by the Stewart et al. (1977) human study was used to derive the acute ReV and ^{acute}ESL for isobutane. The following UFs were applied to the POD_{HEC}:

- 10 for intraspecies variability, and
- a UF_D of 3 for uncertainty associated with an incomplete database because animal toxicity data investigating a complete range of adverse effects was limited. A controlled human inhalation study investigating a complete range of adverse effects with multiple exposure levels and durations, although the exposure concentrations used in this study might be too low. The quality of the key human inhalation study, however, is high. Confidence is considered medium on the database.
- The total UF = 30.

Acute ReV = POD_{HEC} / (UF_H x UF_D)
= 1,000 ppm / (10 x 3)
= 33.3 ppm
= 33,000 ppb (rounded to two significant figures)

The acute ReV for isobutene is very conservative because the exposure concentrations used in this study might be low for isobutane which is of low acute toxicity (i.e., a higher NOAEL may be identified if higher isobutane concentrations were administered). Moreover, no untoward health effects were observed at 1,000 ppm for longer exposure durations of 2 h and 8 h indicating that the NOAEL for 1-h exposure may be conservative if an exposure duration were adjusted from 8 h to 1 h.

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 28,000 ppb (66,000 µg/m^3) for n-butane is based on the acute ReV of 92,000 ppb (220,000 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 4). The ^{acute}ESL of 10,000 ppb (23,000 µg/m^3) for isobutane is based on the acute ReV of 33,000 ppb (78,000 µg/m^3) multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 5).

Table 4. Derivation of the Acute ReV and ^{acute}ESL for n-Butane

Parameter	**Summary**
Study	Hoffman 2008
Study Population	Male and female SD CD rats (10/sex/group)
Study Quality	High
Exposure Method	Exposure via inhalation at 0, 90, 900 or 9,000 ppm (target concentrations)
Critical Effects	Free-standing NOAEL
POD	9,197 ppm (free-standing NOAEL, mean analytical concentration)
Exposure Duration	6 h/d, 7 d/week for two weeks
Extrapolation to 1 h (POD_{ADJ})	9,197 ppm
POD_{HEC}	9,197 ppm
Total uncertainty factors (UFs)	100
Interspecies UF	3
Intraspecies UF	10
LOAEL-to-NOAEL UF	N/A
Incomplete Database UF *Database Quality*	3 Medium
Acute ReV [1 h] (HQ = 1)	**220,000 µg/m3 (92,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**66,000 µg/m3 (28,000 ppb)**

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

Parameter	Summary
Study	Stewart et al. 1977
Study Population	Eight healthy adult male and female volunteers
Study Quality	Medium to high
Exposure Method	Exposure via inhalation at 250, 500, and 1,000 ppm
Critical Effects	Free-standing NOAEL
POD	1,000 ppm (free-standing NOAEL)
Exposure Duration	1 h, 2 h or 8 h
Extrapolation to 1 h (POD_{ADJ})	1,000 ppm
POD_{HEC}	1,000 ppm
Total uncertainty factors (UFs)	30
Interspecies UF	N/A
Intraspecies UF	10
LOAEL-to-NOAEL UF	N/A
Incomplete Database UF *Database Quality*	3 Medium
Acute ReV [1 h] (HQ = 1)	**78,000 µg/m^3 (33,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**23,000 µg/m^3 (10,000 ppb)**

3.6 Welfare-Based Acute ESLs

3.6.1 Odor Perception

Butane has a natural gas or petroleum-like odor. Nagata (2003) reported an odor detection threshold of 1,200 ppm for n-butane. No odor threshold value for isobutane was reported. Since butane and isobutane do not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015a).

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 Short-Term ESL and Values for Air Monitoring Data Evaluations

3.7.1 n-Butane

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

- Acute ReV = 220,000 µg/m^3 (92,000 ppb)
- ^{acute}ESL = 66,000 µg/m^3 (28,000 ppb)

For the evaluation of ambient air monitoring data, the acute ReV of 220,000 µg/m^3 (92,000 ppb) is used (Table 1). The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 66,000 µg/m^3 (28,000 ppb). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.7.2 Isobutane

The acute evaluation resulted in the derivation of the following values for isobutane:

- Acute ReV = 78,000 µg/m^3 (33,000 ppb)
- ^{acute}ESL = 23,000 µg/m^3 (10,000 ppb)

For the evaluation of ambient air monitoring data, the acute ReV of 78,000 µg/m^3 (33,000 ppb) is used for the evaluation of ambient air monitoring data (Table 1).

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 23,000 µg/m^3 (10,000 ppb) (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Physical/Chemical Properties

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

4.2 Noncarcinogenic Potential

Butane is not expected to cause health effects following long-term exposure. Several case reports on human exposure to n-butane were available. Chronic exposure to high concentrations such as long-term abuse of n-butane has been reported to result in irritation, hallucinations, and other symptoms in the CNS (Berzins 1994). However, the case reports of prolonged butane abuse do not provide adequate data for the derivation of toxicity values. No long-term studies using pure butane were located in the available literature. However, there was a subchronic inhalation study of rats exposed to 50:50 mixture of n-butane/n-pentane (Aranyi et al. 1986) and an epidemiological study of kidney function in refinery workers reported by Viau et al. (1987). These studies are briefly described below.

4.2.1 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, 6 h/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. These treatment-related effects included transient hunched posture and/or lethargy and intermittent tremor for n-butane/n-pentane mixtures. 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-d 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 can be considered a free-standing NOAEL. However, since the exposure was 50:50 mixture of n-butane/n-pentane, it was not appropriate to use as the POD to develop chronic toxicity values for n-butane.

4.2.2 Viau et al. (1987) Study

Viau et al. (1987) examined kidney function and damage in 53 male refinery workers exposed to hydrocarbons for an average of 11 years using sensitive biochemical and immunological markers. The results were compared with those of a control group of 61 aged-matched unexposed male employees. The mean concentration of total hydrocarbons containing n-butane, n-pentane, n-hexane and toluene taken from a total of 45 personal monitoring samples ranged from 4,000 to 72,000 µg/m^3. The mean concentration of n-butane, n-pentane, n-hexane, and toluene varied from 400 to 17,800, 200 to 8,800, 300 to 4,500, and 300 to 4,500 µg/m^3, respectively. The study results show that, except for a slight increase in mean albuminuria and urinary excretion of a renal antigen ($p < 0.05$), chronic low-level hydrocarbon exposure does not cause any clinically significant renal abnormalities in exposed workers. Because the refinery workers exposed to a variety of hydrocarbons, it was impossible to relate the observed effect to one compound or one class of components. Thus, the data are inadequate for an assessment of chronic toxicity for n-butane.

Since no chronic toxicity data were available describing the potential chronic toxicity of pure n-butane or isobutane, according to the ESL guidelines, if the minimum database requirements are

not met, then a chronic ReV and ESL are not developed (TCEQ 2006). However, for the purpose of effects evaluations for air permit applications and/or ambient air monitoring data, the chronic ReV of 24,000 µg/m^3 and the chronic ESL of 7,100 µg/m^3 for pentane may be used as a surrogate. The suggested chronic ReV and ESL for butane are based on the analogy of butane and pentane by comparing their LELs (1.8% for butane and 1.4% for pentane) in air and relative toxicities (ACGIH 2001). As indicated in Section 3.1, there is a direct relationship between aliphatic carbon chain length and the potency of alkanes in effects, e.g., butane is relatively less toxic than pentane (Patty and Yant 1929, Stoughton and Lamson 1936, Glowa 1991, Swann et al. 1974, Lammers et al. 2011). Therefore, it is reasonable and health protective to use the chronic ReV of 24,000 µg/m^3 and chronic ESL of 7,100 µg/m^3 for pentane as the chronic ReV and ESL ($^{chronic}ESL_{nonlinear(nc)}$) for butane and isobutane.

4.3 Carcinogenic Potential

No data were found on long-term carcinogenicity studies on n-butane or isobutane. Butane was negative on mutagenicity in *Salmonella typhimurium* strains of bacteria with and without metabolic activation (Shimizu et al. 1985, as cited in Berzins 1994; Kirwin et al. 1908, as cited in Galvin 1999). The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of this chemical. The American Conference of Governmental Industrial Hygienists (ACGIH) has not assigned a carcinogenicity designation to this chemical. The US National Toxicology Program (NTP) has not listed this chemical in its report on carcinogens. According to the Guidelines for Carcinogen Risk Assessment (USEPA, 2005), the database for butane and isobutane provides "inadequate information to assess carcinogenic potential." Because there are no available data to assess carcinogenicity in humans or animals, the $^{chronic}ESL_{linear(c)}$ was not developed (EU 2003).

4.4 Welfare-Based Chronic ESL

No information was found to indicate that special consideration should be given to possible chronic vegetation effects from n-butane or isobutane.

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

As indicated in Section 4.2, the following chronic ReV and ESL are used for n-butane, which are based on the values derived for pentane:

- Chronic ReV = 24,000 µg/m^3 (10,000 ppb), as pentane
- $^{chronic}ESL_{nonlinear(nc)}$ = 7,100 µg/m^3 (3,000 ppb), as pentane

For the evaluation of ambient air monitoring data, the chronic ReV of 24,000 µg/m^3 (10,000 ppb), as pentane, is used (Table 1).

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ of 7,100 µg/m^3 (3,000 ppb), as pentane (Table 2).

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