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1-Butene

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Prepared by

Roberta L. Grant, Ph.D.

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADH	aldehyde dehydrogenase
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
⁰ C	degrees centigrade
BMR	benchmark response
CNS	central nervous system
ConA	Concanavalin A
DSD	development support document
EC ₅₀	Effective concentration at a 50% response level
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 _{threshold(c)}	chronic health-based Effects Screening Level for threshold dose response cancer effect
^{chronic} ESL _{threshold(nc)}	chronic health-based Effects Screening Level for threshold dose response noncancer effects
^{chronic} ESL _{nonthreshold(c)}	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
^{chronic} ESL _{nonthreshold(nc)}	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
^{chronic} ESL _{veg}	chronic vegetation-based Effects Screening Level
EU	European Union
GC	gas chromatography

GLP	good laboratory practice
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
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IC ₅₀	Inhibitory concentration at a 50% response level
IL	interleukin
IOAEL	inhalation observed adverse effect level
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LC ₅₀	concentration causing lethality in 50% of test animals
LD ₅₀	dose causing lethality in 50% of test animals
LPS	lipopolysaccharide
LOAEL	lowest-observed-adverse-effect-level
LTD	Limited toxicity data
MW	molecular weight
µg	microgram
µg/m ³	micrograms per cubic meter of air
mg	milligrams
mg/m ³	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number
NAC	National Advisory Committee

NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
POD	point of departure
POD _{ADJ}	point of departure adjusted for exposure duration
POD _{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
RD ₅₀	50% reduction in respiration rate
ReV	reference value
RGDR	regional gas dose ratio
ROS	Reactive oxygen species
RP	Relative potency
RP _{GM}	Geometric mean of relative potency endpoints
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

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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 1-butene. Please refer to Section 1.6.2 of the [TCEQ 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 1-butene's physical/chemical data.

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

Short-Term Values	Concentration	Notes
Acute ReV	Short-Term Health 62,000 $\mu\text{g}/\text{m}^3$ (27,000 ppb)	Critical Effect: Based on free-standing NOAEL, no adverse effects observed in Sprague-Dawley rats in a repeat dose, subacute study. High concentrations produce CNS effects
^{acute} ESL _{odor}	Odor 820 $\mu\text{g}/\text{m}^3$ (360 ppb)	50% detection threshold, gas-house odor (i.e., slight olefinic odor, slightly aromatic odor)
^{acute} ESL _{veg}	- - -	Concentrations producing vegetative effects were significantly above other values
Long-Term Values	Concentration	Notes
Chronic ReV	Long-Term Health 5,300 $\mu\text{g}/\text{m}^3$ (2,300 ppb)	Critical Effect(s): Based on free-standing NOAEL, no adverse effects observed in Sprague-Dawley rats in a repeat dose, subacute study
^{chronic} ESL _{nonthreshold(c)} ^{chronic} ESL _{threshold(c)}	- - -	No data found
^{chronic} ESL _{veg}	- - -	No data found

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute} ESL [1 h] (HQ = 0.3)	19,000 $\mu\text{g}/\text{m}^3$ (8,100 ppb) ^a	Critical Effect: Based on free-standing NOAEL, no adverse effects observed in Sprague-Dawley rats in a repeat dose, subacute study. High concentrations produce CNS effects
^{acute} ESL _{odor}	820 $\mu\text{g}/\text{m}^3$ (360 ppb) Short-Term ESL for Air Permit Reviews	50% detection threshold, gas-house odor (i.e., slight olefinic odor, slightly aromatic odor)
^{acute} ESL _{veg}	---	Insufficient data
Long-Term Values	Concentration	Notes
^{chronic} ESL _{threshold(nc)} (HQ = 0.3)	Long-Term ESL for Air Permit Reviews 1,600 $\mu\text{g}/\text{m}^3$ (690 ppb) ^b	Critical Effect(s): Based on free-standing NOAEL, no adverse effects observed in Sprague-Dawley rats in a repeat dose, subacute study
^{chronic} ESL _{nonthreshold(c)} ^{chronic} ESL _{threshold(c)}	---	No data found
^{chronic} ESL _{veg}	---	No data found

^a Based on the acute ReV of 62,000 $\mu\text{g}/\text{m}^3$ (27,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

^b Based on the chronic ReV of 5,300 $\mu\text{g}/\text{m}^3$ (2,300 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CH ₂ =CHCH ₂ CH ₃	OECD 2004
Chemical Structure		chemIDplus Lite
Molecular Weight	56.11	TRRP 2006
Physical State at 25°C	Gas	TRRP 2006
Color	Colorless	OECD 2004
Odor	Gas-house odor (slight olefinic odor, slightly aromatic odor)	Katz and Talbert 1930
CAS Registry Number	106-98-9	TRRP 2006
Synonyms	1-butylene, butane-1, but-1-ene, n-butene, n-butylene, ethyethylene, alsph-butene, alpha-butylene, 1-buten, buten-(1), butylen, butylen-(1), n-buten-1, buten (technisch)	OECD 2004
Solubility in water	239.69 mg/L	TRRP 2006
Log K _{ow}	2.45	TRRP 2006
Vapor Pressure	1609.91 mm Hg	TRRP 2006
Relative Density	0.5879 g/cm ³	OECD 2004
Melting Point	-185.3°C	OECD 2004
Boiling Point	-6.2°C	OECD 2004
Conversion Factors	1 ppb = 2.29 µg/m ³ 1 µg/m ³ = 0.437 ppb	Toxicology Division

Chapter 2 Major Sources and Uses

The following information was obtained from the Organization for Economic Cooperation and Development (OECD 2004):

Butenes are a component of natural gas and crude oil. Although butenes have been identified in natural environments, this has traditionally been associated with losses from petrogenic sources resulting from offgassing or venting (e.g. underwater or near-shore oil seepage). Trace levels of butenes can be identified in urban and suburban air arising from combustion of fossil fuels and losses from gas plants and refineries. (OECD 2004)

1-Butene can be produced by cracking of petroleum products. It is used as an intermediate in the production of a wide variety of chemicals and is found in gasoline. It is also used as a monomer or copolymer in the production of synthetic rubber.

Estimated United States production of 1-butene was 11,770 million pounds (5,300 kilotons) in 2001 (SIAP 2004).

Chapter 3 Acute Evaluation

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

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

1-Butene is a flammable, colorless gas. The log K_{ow} (2.45), moderate water solubility (239.69 milligram per liter (mg/L)), and low molecular weight (56.11) indicate the potential for 1-butene to be absorbed via the lungs and widely distributed within the body. The lower explosive limit for the butenes category is greater than 8,000 ppm. Other physical/chemical properties of 1-butene can be found in Table 3.

3.1.1.2 Key and Supporting Studies

This section is based on information on 1-butene obtained from OECD (2004) as well as a search of the literature since 2000. 1-Butene is an anesthetic (about 4.5 times more potent than ethylene) at concentrations above the flammability range. The main effects produced after exposure to high concentrations of 1-butene are central nervous system (CNS) depression, anesthesia, and/or asphyxiation.

3.1.1.2.1 Rat Studies

The following effects as reported in OECD (2004) have been observed in rats after exposure to 1-butene:

- at 15% (150,000 ppm), rats showed reversible signs of incoordination, confusion, and hyperexcitability;
- at 20% (200,000 ppm), anesthesia occurred in 8-15 minute (min), with subsequent respiratory failure in 2 hour (h);
- at 30% (300,000 ppm), deep anesthesia occurred in 2-4 min and respiratory failure in 40 min;
- at 40% (400,000 ppm), profound anesthesia occurred in 30 second without CNS symptoms, and death occurred in 10-15 min.

The anesthetic dose of butene is only slightly below the toxic or lethal dose (Miller 1978 in OECD 2004). There have not been any acute toxicity studies, such as LC₅₀ studies, conducted on 1-butene although the acute toxicity of 1-butene is of low order (i.e., at 20% 1-butene, respiratory failure occurred in 2 h).

However, a combined repeated-exposure, reproduction and neurotoxicity screening study conducted in rats via whole-body inhalation exposure sponsored by the American Chemistry Council (ACC 2003) and conducted by Huntingdon Life Sciences was selected as the key study and used to derive a conservative 1-h ReV for 1-butene. The study was conducted using the following guidelines:

- USEPA Good Laboratory Practices (GLP) as set forth in 40 CFR Part 792 (TSCA) and OECD GLP; and
- The OECD Guideline for Testing of Chemicals, Guideline 422, Combined Repeated Exposure Toxicity Study with Reproduction/Development Toxicity Screening Test.

To study the effects in adult male and female rats, the test substance was administered to Sprague Dawley rats (12/sex/F₀ group) at target concentrations of 500, 2,000 and 8,000 ppm for 6 h/day, 7 days/week for 2 weeks before mating initiation. Exposure of F₀ males (12/group) continued for a minimum exposure of 28 days (during mating and post-mating until they were euthanized), while F₀ females (12/group) were exposed once daily (6 hours/day, 7 days/week) for 28 days. In addition, a control group (12 males and 12 females) received nitrogen enriched air only while in the chamber. Exposure levels were determined using an on-line gas chromatograph four times per chamber per day. A wide variety of health effects were evaluated: viability checks, physical observations, body weight measurements, and feed consumption measurements; hematology, coagulation, and clinical chemistry; organ/body weight and organ/brain weight ratios; complete macroscopic postmortem examinations and histopathological evaluations on selected tissues conducted on selected animals; and motor activity or functional observational battery parameters. There were no adverse 1-butene related effects on any parameter measured at any concentration. In comparison with controls, there was a slightly increased incidence and severity of mixed inflammatory cells in the cecal mucosa of rats exposed to 1-butene at exposure levels of 2,000 ppm and above. However, according to the study authors, the increased incidence is unlikely to be related to treatment with 1-butene.

To study reproductive/developmental effects, the test substance was administered as described previously and satellite females (12/group) continued to be treated once daily (6 h/day) during mating, and then once daily (6 h/day) during gestation days 0-19. There were no adverse 1-butene-related effects observed in the reproductive systems or on any other parameter measured at any concentration in the parental (F_0) generation. Pups (F_1 generation) were observed as soon as possible after parturition for their sex, the number of live and dead pups and pup abnormalities. Thereafter, litters were observed twice daily (morning and afternoon) and gross physical examinations were performed on lactation days 0 and 4. Pups were sexed on lactation day 0 and sex was verified on lactation day 4. Individual pup body weights were recorded on lactation days 1 and 4. Pups surviving until lactation day 4 were euthanized followed by a macroscopic postmortem examination (external), in which any unusual abnormalities were noted.

All mated female animals (except one animal in the 2,000 ppm group) became pregnant and delivered live pups. Mating indices for the male rats treated with 1-butene were comparable to the control group. Mating, fertility, and gestation indices for the female rats treated with 1-butene were comparable to the control group. Most of the females in each group mated at the first opportunity. There were also no treatment-related differences in the other reproductive parameters up to the time of parturition, including the percent of females completing delivery and the duration of gestation, when compared to the control group. There were no treatment-related differences in all parturition parameters, including the total number of pups delivered, the number of pups dying, the viability (4 day survival) index, the number of implantation sites and corpora lutea per dam, the pup sex ratio and the number of live pups/litter, when compared to the control group. The pups were unremarkable during the lactation period. There were no exposure-related differences in body weights or weight gains in the pups feeding from test article exposed animals compared to the pups feeding from control animals. There were no exposure-related differences in macroscopic postmortem evaluations in the pups feeding from test article exposed animals compared to the pups feeding from control animals.

Thus, the free-standing NOAEL for 1-butene for adult rats and for reproductive/developmental effects was $> 8,000$ ppm (ACC 2003). The mean (\pm standard deviation) analytical (gas chromatography) concentrations for the control and the exposure groups were as follows: 0 ± 0 , 524 ± 40 , $2,062 \pm 126$, and $8,271 \pm 683$ ppm. The mean analytical concentration of 8,271 ppm will be used as the free-standing NOAEL.

3.1.1.2.2 Mouse Study

The following effects as reported in ACC (2001) have been observed in mice after exposure to 1-butene for 10 minutes:

- 227,000 ppm (22.7%) induced surgical anesthesia in mice within 10 minutes (Virtue 1950 in ACC 2001)
- 272,000 ppm (27.2%) produced respiratory arrest in mice (Virtue 1950 in ACC 2001)

1-Butene was evaluated *in vivo* for its ability to induce micronuclei in bone marrow polychromatic erythrocytes (PCEs) in male and female Crl:CDR (IRC)Br Swiss mice (OECD 2004). Although the purpose of the study was to evaluate mutagenicity of 1-butene, very limited health effects data was provided. Groups of ten male and female mice were exposed to 1-butene in an inhalation chamber at concentrations of 0, 1,000, 9,000, or 22,000 ppm 2 h/day for 2 days. One half of each group was sacrificed on day 3 and the remainder on day 4 following exposure. One group of 15 male and female mice exposed for one day to 22,000 ppm was sacrificed on days 2, 3, and 4 after treatment (5/sex/day). Test concentrations were monitored each day by gas chromatography. Health-effects data collected included group mean body weights for each day. Mice at all doses were unconscious during exposure to 1-butene but recovered when exposure ended. No other clinical signs were observed and no mortality occurred at any dose level.

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

Effects occurring at the lowest concentration are reversible signs of incoordination, confusion, and hyperexcitability in rats (i.e., CNS effects). The mode of action (MOA) for CNS effects has not been clearly established but may be related to solvent effects on lipid and fatty acid compositions of membranes. The CNS effects observed in rats (Section 3.1.1.2.1) suggest that concentration and duration play a role in 1-butene effects.

In the reproductive/developmental/neurotoxicity study selected as the key study, data on the exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), the exposure concentration of the parent chemical was used as the default dose metric.

3.1.3 Point of Departure (POD) for Key Study and Dosimetric Adjustments

The free-standing NOAEL in rats of 8,271 ppm (analytical) reported from a subacute, repeat dose study is used as the animal POD (ACC 2003). The mouse study described in Section 3.1.1.2.2 was not used as a key study because of the limited health effects data that were reported and limited information on how the study was conducted.

3.1.3.1 Default Exposure Duration Adjustments

The POD obtained from the ACC (2003) study is a free-standing NOAEL based on an exposure duration of 6 h/day. The acute ReV is used to evaluate a 1-h exposure. A duration adjustment from the longer exposure study to the desired averaging time (i.e., 6 h to 1 h) was not conducted since there was no existing data on shorter durations to show that the adjustment was scientifically defensible (TCEQ 2012).

3.1.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

1-Butene causes CNS effects, which are systemic rather than point-of-entry respiratory effects. In addition, the physical/chemical parameters of 1-butene indicate the potential for 1-butene to be absorbed via the lungs and widely distributed within the body (Section 3.1.1.1). 1-Butene was therefore considered a Category 3 gas (USEPA 1994). For Category 3 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

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

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient

A = animal

H = human

For 1-butene, the blood:gas partition coefficients for rat and human are unknown. Therefore, a default value of 1 is used for $(H_{b/g})_A / (H_{b/g})_H$. The $(H_{b/g})_A / (H_{b/g})_H$ is the regional gas dose ratio (RGDR) (USEPA 1994).

$$\begin{aligned} POD_{HEC} &= POD_{ADJ} \times RGDR \\ &= 8,271 \text{ ppm} \times 1 = 8,271 \text{ ppm} \end{aligned}$$

3.1.4 Adjustments of the POD_{HEC}

Since the MOA by which 1-butene produces toxicity is not understood, the default for noncarcinogenic effects is to determine a POD and apply uncertainty factors (UFs) to derive a ReV (i.e., assume a threshold/nonlinear MOA). The following UFs were applied to the POD_{HEC} of 8,271 ppm: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), and 10 for database uncertainty (UF_D), for a total $UF = 300$:

- A UF_H of 10 was used to account for variation in sensitivity among members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences. There are no data to indicate that a UF_H larger than 10 is needed to protect children or other potentially sensitive subpopulations.
- A UF_A of 3 was used because a default dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences.
- A UF_D of 10 was used, because data from a high-quality toxicity study is available for only one species, the rat. A micronucleus mutagenicity assay conducted in mice indicates that mice may be more sensitive than rats. The quality of the rat study is high and the confidence in the acute database is low to medium.

$$\begin{aligned}\text{acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_A \times \text{UF}_D) \\ &= 8,271 \text{ ppm} / (10 \times 3 \times 10) \\ &= 27.57 \text{ ppm} \\ &= 27,570 \text{ ppb}\end{aligned}$$

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

The acute ReV value was rounded to two significant figures. The resulting 1-h acute ReV is 27,000 ppb (62,000 $\mu\text{g}/\text{m}^3$). The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 8,100 ppb (19,000 $\mu\text{g}/\text{m}^3$) (Table 4). The acute ReV and ^{acute}ESL are believed to be conservative since a free-standing NOAEL from a subacute study was used and a duration adjustment from 6 h to 1 h was not conducted.

Table 4. Derivation of the Acute ReV and ^{acute}ESL

Parameter	Summary
Study	Combined repeated-exposure, reproduction and neurotoxicity screening study (ACC 2003)
Study population	Sprague Dawley male and female rats (12/sex/concentration)
Study quality	High
Exposure methods	Exposures via inhalation at 0, 500, 2,000 and 8,000 ppm (analytical 0 ± 0 , 524 ± 40 , $2,062 \pm 126$, and $8,271 \pm 683$ ppm)
Critical effects	Free-standing NOAEL, no observed effects in parental (F ₀) or in offspring (F ₁) generation. High concentrations produce CNS effects.
POD	8,271 ppm (free-standing NOAEL)
Exposure duration	6 h/day, 7 days/week for approximately 28-42 days
Extrapolation to 1 h	No adjustment since the POD was a free-standing NOAEL (TCEQ 2012)
POD _{ADJ} (1 h)	8,271 ppm
POD _{HEC}	8,271 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	300
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	Not applicable
<i>Incomplete Database UF</i>	10
<i>Database Quality</i>	Low to medium
acute ReV [1 h] (HQ = 1)	62,000 µg/m³ (27,000 ppb)
^{acute}ESL [1 h] (HQ = 0.3)	19,000 µg/m³ (8,100 ppb)

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Katz and Talbert (1930 as reported in van Gemert 2003) reported 1-butene to have a “gas-house” odor (i.e., slight olefinic odor, slightly aromatic odor) and report a 50% odor detection threshold of $2,100 \mu\text{g}/\text{m}^3$ (920 ppb). The 50% odor detection threshold for 1-butene determined by Nagata (2003) using the triangular odor bag method was $820 \mu\text{g}/\text{m}^3$ (360 ppb). Nagata (2003) is a Level 1 odor source whereas Katz and Talbert (1930) is a Level 3 odor source (TCEQ 2012). Since the value of $820 \mu\text{g}/\text{m}^3$ (360 ppb) reported by Nagata (2003) is a Level 1 odor source, it is the $^{\text{acute}}\text{ESL}_{\text{odor}}$. Odor is a concentration-dependent effect, so the same 1-h $^{\text{acute}}\text{ESL}_{\text{odor}}$ is assigned to all averaging times.

3.2.2 Vegetation Effects

1-Butene concentrations that produce vegetative effects, such as abscission and inhibition of growth, are orders of magnitude higher than concentrations of ethylene, propylene, and acetylene that produce similar effects (USDHEW 1970). Since concentrations producing vegetative effects ($> 10,000$ ppm) are significantly above other health- and odor-based concentrations, an $^{\text{acute}}\text{ESL}_{\text{veg}}$ was not developed for 1-butene.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

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

- acute ReV = $62,000 \mu\text{g}/\text{m}^3$ (27,000 ppb)
- $^{\text{acute}}\text{ESL}$ = $19,000 \mu\text{g}/\text{m}^3$ (8,100 ppb)
- $^{\text{acute}}\text{ESL}_{\text{odor}}$ = $820 \mu\text{g}/\text{m}^3$ (360 ppb)

The short-term ESL for air permit evaluations is the $^{\text{acute}}\text{ESL}_{\text{odor}}$ of $820 \mu\text{g}/\text{m}^3$ (360 ppb) as it is lower than the $^{\text{acute}}\text{ESL}$ (Table 2). For the evaluation of ambient air monitoring data, the $^{\text{acute}}\text{ESL}_{\text{odor}}$ of $820 \mu\text{g}/\text{m}^3$ (360 ppb) is lower than the acute ReV of $62,000 \mu\text{g}/\text{m}^3$ (27,000 ppb) (Table 1), although both values may be used for the evaluation of air data. The $^{\text{acute}}\text{ESL}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data (TCEQ 2012).

3.4. Acute Observed Adverse Effect Level

1-Butene has limited toxicity data (i.e., only a free-standing NOAEL of 8,271 ppm and concentrations that cause severe adverse effects were identified) so an acute inhalation observed adverse effect level was not determined.

Chapter 4 Chronic Evaluation

4.1 *Noncarcinogenic Potential*

4.1.1 Physical/Chemical Properties

Physical/chemical properties for 1-butene are discussed in Chapter 3. Since the log K_{ow} for 1-butene is 2.45, significant bioaccumulation is not expected (an increase in the potential to bioaccumulate in organisms is associated with an increase in $\log K_{ow} \geq 4$ (TCEQ 2012)).

4.1.2 Key Study

No subchronic or chronic toxicity studies were available describing the potential chronic toxicity of 1-butene. However, a combined repeated-exposure, reproduction and neurotoxicity screening study conducted in rats via whole-body inhalation exposure was sponsored by the American Chemistry Council (ACC 2003). This study is described in Section 3.1.1.2.1 and was selected as the key study used to develop a chronic ReV for 1-butene. Significant bioaccumulation of 1-butene is not expected and no health effects were observed in the subacute study at 8,000 ppm.

This is supported by acute, subacute, and chronic toxicity studies available for isobutene (TCEQ 2008), a butene isomer. For isobutene, a subacute reproductive/developmental study (CTL 2002 in OECD 2004) and a 14-week study in F344/N rats and B6C3F1 mice (NTP 1998) had a free-standing NOAEL of 8,000 ppm. The 2-year bioassays (NTP 1998) conducted in F344/N rats and B6C3F1 mice also had a free-standing NOAEL of 8,000 ppm. At much higher concentrations, isobutene causes CNS effects.

The main findings from the ACC (2003) study were exposure to 1-butene at concentrations up to 8,000 ppm did not induce significant systemic toxicity in male rats exposed for 39-46 days, or in pregnant female rats exposed for 2 weeks pre-mating, through mating and gestation to day 19 (ACC 2003). No developmental effects were noted. Thus, the free-standing NOAEL for 1-butene for adult rats and for reproductive/developmental effects was $> 8,000$ ppm (ACC 2003). The mean (\pm standard deviation) analytical (gas chromatography) concentrations for the control and the exposure groups were as follows: 0 ± 0 , 524 ± 40 , $2,062 \pm 126$, and $8,271 \pm 683$ ppm. The mean analytical concentration of 8,271 ppm will be used as the free-standing NOAEL.

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

Anesthesia, narcosis, and other CNS effects were critical effects for 1-butene after acute exposure at high concentrations (3.1.1.2 Key and Supporting Studies), although these effects may not be relevant for low-level chronic exposure. The critical effects after chronic exposure are unknown since there are no chronic studies for 1-butene. The presence of the double bond makes 1-alkenes optimal substrates for the cytochrome P450 enzymes that convert them to the respective reactive epoxides that possess alkylating capacity towards nucleophilic sites in proteins and DNA (Eide et al. 1995). The epoxides may be rapidly metabolized by epoxide hydrolase (EH) and glutathione-S-transferase (GST) and detoxified. Information on the metabolism of 1-butene is unknown.

4.1.3.2 Eide et al. (1995)

Eide et al. (1995) investigated the toxicokinetics of individual C2-C8 1-alkenes as well as measuring hemoglobin and DNA adducts to evaluate genotoxicity and reactivity. Male SD rats were exposed to 300 ppm of the individual alkenes for 12 h/day for three consecutive days. Chamber concentrations were evaluated by gas chromatography. Immediately after exposure, concentrations of the 1-alkenes in blood and tissues (liver, lung, brain, kidneys, and fat) were measured to evaluate toxicokinetics. Hemoglobin adducts in blood (N-(2-hydroxyalkyl)valine) and DNA adducts in lymphocytes and liver (7-alkylguanine) were also determined.

4.1.3.2.1 Toxicokinetics

The concentration of 1-butene and other 1-alkenes was lowest in blood and highest in fat tissue. A steady-state level was reached during the first 12-h exposure, since no systemic increase or decrease of alkene levels occurred in any organ from the first to the third exposure. Twelve hours after the last exposure, 1-butene concentrations in blood and tissues were low. Concentrations of C2-C8 1-alkenes in blood and different tissues increased with increasing number of carbon atoms.

4.1.3.2.2 Hemoglobin and DNA Adducts

All 1-alkenes caused formation of detectable levels of hemoglobin and DNA adducts, although the levels of hemoglobin adducts after 1-butene exposure were low when compared to ethene and propene, which had the highest levels of adducts (Table 5). Levels of hemoglobin and DNA adducts, a general measure of reactivity, decreased with increasing number of carbon atoms. Table 5 provides data on hemoglobin and DNA adducts from Eide et al. (1995).

Table 5 Hemoglobin and DNA Adducts for C2-C6 Alkenes ^a

1-Alkene	Hemoglobin ^b	Lymphocytes ^c	Liver ^c
ethene	2730 ± 100	5.8 ± 2.2	7.4 ± 1.0
propene	740 ± 50	1.8 ± 0.9	2.8 ± 0.9
1-butene	20 ± 1	0.8 ± 0.4	2.1 ± 0.5
1-pentene	51 ± 3	0.5 ± 0.2	1.8 ± 0.6
1-hexene	39 ± 1	0.3 ± 0.3	1.4 ± 0.2

^a Levels (mean ± SD) of N-(2-hydroxyalkyl)valine in hemoglobin (pmol/g) and 7-alkylguanine in lymphocytes and liver (adducts/ 10⁷ normal nucleotides). Background values have been subtracted.

^b n = 3-8 for hemoglobin adduct analyses

^c n = 4 for DNA adduct analyses

4.1.3.3 Dose Metric

In the reproductive/developmental/neurotoxicity study selected as the key study, data on the exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), the exposure concentration of the parent chemical was used as the default dose metric.

4.1.4 Point of Departure (POD) for Key Study and Dosimetric Adjustments

The free-standing NOAEL in rats of 8,271 ppm (analytical) reported from a subacute, repeat dose study is used as the animal POD (ACC 2003). The critical effect is unknown.

4.1.4.1 Default Exposure Duration Adjustments

Even though the POD was a free-standing NOAEL, an adjustment from a discontinuous (6 h/day; 7 days/week) to a continuous exposure duration was conducted as discussed in TCEQ (2012):

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

where:

POD = POD from animal study based on discontinuous exposure regimen

D = exposure duration (hours per day)

F = exposure frequency (days per week)

$$POD_{ADJ} = 8,271 \times (6/24 \text{ h}) \times (7/7 \text{ days})$$

$$POD_{ADJ} = 2,068 \text{ ppm}$$

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The physical/chemical parameters of 1-butene indicate the potential for 1-butene to be absorbed via the lungs and widely distributed within the body (Section 3.1.1.1). Although the critical effect after chronic exposure to 1-butene is unknown, systemic rather than point-of-entry respiratory effects are more likely. 1-Butene was therefore considered a Category 3 gas (USEPA 1994). For Category 3 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

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

where:

$H_{b/g}$ = ratio of the blood:gas partition coefficient

A = animal

H = human

For 1-butene, the blood:gas partition coefficients for rat and human are unknown. Therefore, a default value of 1 is used for $(H_{b/g})_A / (H_{b/g})_H$. The $(H_{b/g})_A / (H_{b/g})_H$ is the regional gas dose ratio (RGDR) (USEPA 1994).

$$\begin{aligned} \text{POD}_{\text{HEC}} &= \text{POD}_{\text{ADJ}} \times \text{RGDR} \\ &= 2,068 \text{ ppm} \times 1 = 2,068 \text{ ppm} \end{aligned}$$

4.1.5 Adjustments of the POD_{HEC}

Since the MOA by which 1-butene produces toxicity is not understood, the default for noncarcinogenic effects is to determine a POD and apply uncertainty factors (UFs) to derive a ReV (i.e., assume a threshold/nonlinear MOA). The following UFs were applied to the POD_{HEC} of 2,068 ppm: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), 3 for use of a subacute study (UF_{Sub}) and 10 for database uncertainty (UF_D), for a total $\text{UF} = 900$:

$$\begin{aligned} \text{acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_A \times \text{UF}_{\text{Sub}} \times \text{UF}_D) \\ &= 2,068 \text{ ppm} / (10 \times 3 \times 3 \times 10) \\ &= 2.298 \text{ ppm} \\ &= 2,300 \text{ ppb (rounded to two significant figures)} \end{aligned}$$

- A UF_H of 10 was used to account for variation in sensitivity among members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences. There are no data to indicate that a UF_H larger than 10 is needed to protect children or other potentially sensitive subpopulations.
- A UF_A of 3 was used because a default dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences.
- A UF_{Sub} of 3 was used to account for the use of a subacute study (39-46 days) to develop a chronic ReV. A larger UF_{Sub} was not used because 1-butene is not expected to bioaccumulate.
- A UF_D of 10 was used, because toxicity data is available for only one species. The quality of the rat study is high and the confidence in the chronic database is low.

4.1.6 Health-Based Chronic ReV and ^{acute}ESL

The chronic ReV value was rounded to two significant figures. The resulting chronic ReV is 2,300 ppb (5,300 $\mu\text{g}/\text{m}^3$). The rounded chronic ReV was then used to calculate

the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient (HQ) of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 690 ppb ($1,600 \mu\text{g}/\text{m}^3$) (Table 6).

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

Parameter	Summary
Study	Combined repeated-exposure, reproduction and neurotoxicity screening study (ACC 2003)
Study population	Sprague Dawley male and female rats (12/sex/concentration)
Study quality	High
Exposure methods	Exposures via inhalation at 0, 500, 2,000 and 8,000 ppm (analytical 0 ± 0 , 524 ± 40 , $2,062 \pm 126$, and $8,271 \pm 683$ ppm)
Critical effects	No observed effects in parental (F_0) or in offspring (F_1) generation. High concentrations produce CNS effects
POD	8,271 ppm (free standing NOAEL)
Exposure duration	6 h/day, 7 days/week for approximately 28-42 days
POD _{ADJ} (continuous exposure)	2,068 ppm
POD _{HEC}	2,068 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	900
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>Subchronic UF</i>	3
<i>LOAEL UF</i>	Not applicable
<i>Incomplete Database UF</i>	10
<i>Database Quality</i>	Low
chronic ReV (HQ = 1)	$5,300 \mu\text{g}/\text{m}^3$ (2,300 ppb)
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	$1,600 \mu\text{g}/\text{m}^3$ (690 ppb)

4.2 Carcinogenic Potential

There are no human or animal studies indicating that 1-butene has carcinogenic potential so a chronic carcinogenic value was not developed. Data from *in vitro* and *in vivo* mutagenicity assays indicate 1-butene is not mutagenic.

4.2.1 In Vitro Mutagenicity

1-Butene was tested in an Ames assay in 4 strains of *Salmonella typhimurium* (i.e., TA98, TA100, TA1535, TA1537) with and without metabolic activation and in *Escherichia coli* WP2 uvrA (Araki et al. 1994 in OECD 2004). 1-Butene did not induce mutagenic events in any strain in this assay with or without metabolic activation.

4.2.2 In Vivo Mutagenicity

1-Butene was evaluated *in vivo* for its ability to induce micronuclei in bone marrow polychromatic erythrocytes (PCEs) in male and female Crl:CDR (IRC) Br Swiss mice. 1-Butene was premixed with ambient air and introduced into inhalation chambers containing groups of mice (10 M, 10 F) at concentrations of 0, 1000, 9000, or 22,000 ppm 2 h/day for 2 days. Test concentrations were monitored each day by gas chromatography. Inhalation of 1-butene by mice did not induce significant changes in micronucleus formation in bone marrow polychromatic erythrocytes or normochromatic erythrocytes and did not cause significant changes in the ratio of PCE/NCE (reported in OECD 2004).

4.3. Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- chronic ReV = 5,300 $\mu\text{g}/\text{m}^3$ (2,300 ppb)
- $\text{chronic ESL}_{\text{threshold(nc)}} = 1,600 \mu\text{g}/\text{m}^3$ (690 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 5,300 $\mu\text{g}/\text{m}^3$ (2,300 ppb) is used (Table 1). The long-term ESL for air permit evaluations is the $\text{chronic ESL}_{\text{threshold(nc)}}$ of 1,600 $\mu\text{g}/\text{m}^3$ (690 ppb) (Table 2). The $\text{chronic ESL}_{\text{threshold(nc)}}$ (HQ = 0.3) is not used for evaluation of air monitoring data (TCEQ 2012).

4.5. Chronic Inhalation Observed Adverse Effect Level

1-Butene has no chronic toxicity data so a chronic inhalation observed adverse effect level was not determined.

Chapter 5. References

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