



Development Support Document  
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## **2-Butene (Cis and Trans)**

**CAS Registry Number: 107-01-7**

### **Cis-2-Butene**

**CAS Registry Number: 590-18-1**

### **Trans-2-Butene**

**CAS Registry Number: 624-64-6**

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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
<sup>0</sup> C	degrees centigrade
BMR	benchmark response
CNS	central nervous system
ConA	Concanavalin A
CRO	crotonaldehyde
DSD	development support document
EC <sub>50</sub>	Effective concentration at a 50% response level
ESL	Effects Screening Level
<sup>acute</sup> ESL	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
<sup>acute</sup> ESL <sub>generic</sub>	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
<sup>acute</sup> ESL <sub>odor</sub>	acute odor-based Effects Screening Level
<sup>acute</sup> ESL <sub>veg</sub>	acute vegetation-based Effects Screening Level
<sup>chronic</sup> ESL <sub>threshold(c)</sub>	chronic health-based Effects Screening Level for threshold dose response cancer effect
<sup>chronic</sup> ESL <sub>threshold(nc)</sub>	chronic health-based Effects Screening Level for threshold dose response noncancer effects
<sup>chronic</sup> ESL <sub>nonthreshold(c)</sub>	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
<sup>chronic</sup> ESL <sub>nonthreshold(nc)</sub>	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
<sup>chronic</sup> ESL <sub>veg</sub>	chronic vegetation-based Effects Screening Level

<b>Acronyms and Abbreviations Definition</b>	
EU	European Union
GC	gas chromatography
GLP	good laboratory practice
hr	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 <sub>50</sub>	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 <sub>50</sub>	concentration causing lethality in 50% of test animals
LD <sub>50</sub>	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 <sup>3</sup>	micrograms per cubic meter of air
mg	milligrams
mg/m <sup>3</sup>	milligrams per cubic meter of air
min	minute

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<b>Acronyms and Abbreviations Definition</b>	
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 <sub>ADJ</sub>	point of departure adjusted for exposure duration
POD <sub>HEC</sub>	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
RD <sub>50</sub>	50% reduction in respiration rate
ReV	reference value
RGDR	regional gas dose ratio
ROS	Reactive oxygen species
RP	Relative potency
RP <sub>GM</sub>	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 <sub>H</sub>	interindividual or intraspecies human uncertainty factor
UF <sub>A</sub>	animal to human uncertainty factor

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**Acronyms and Abbreviations Definition**

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$UF_{Sub}$	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

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## 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 2-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 2-butene's physical/chemical data.

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

<b>Short-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
Acute ReV	<b>Short-Term Health 34,000 <math>\mu\text{g}/\text{m}^3</math> (15,000 ppb)</b>	<b>Critical Effect:</b> Decreased body weight in female Wistar rats observed after seven days in a reproductive/developmental study
<sup>acute</sup> ESL <sub>odor</sub>	<b>Odor 4,800 <math>\mu\text{g}/\text{m}^3</math> (2,100 ppb)</b>	50% detection threshold, gas-house odor (i.e., slight olefinic odor, slightly aromatic odor)
<sup>acute</sup> ESL <sub>veg</sub>	- - -	Concentrations producing vegetative effects were significantly above other values
<b>Long-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
Chronic ReV	<b>Long-Term Health 1,600 <math>\mu\text{g}/\text{m}^3</math> (690 ppb)</b>	<b>Critical Effect(s):</b> Decreased body weight in Wistar rats observed in a subacute reproductive/developmental study
<sup>chronic</sup> ESL <sub>nonthreshold(c)</sub>	- - -	No data found
<sup>chronic</sup> ESL <sub>threshold(c)</sub>	- - -	No data found
<sup>chronic</sup> ESL <sub>veg</sub>	- - -	No data found

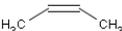
**Table 2. Air Permitting Effects Screening Levels (ESLs)**

<b>Short-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
<sup>acute</sup> ESL [1 h] (HQ = 0.3)	10,000 $\mu\text{g}/\text{m}^3$ (4,500 ppb) <sup>a</sup>	<b>Critical Effect:</b> Decreased body weight in female Wistar rats observed after seven days in a reproductive/developmental study
<sup>acute</sup> ESL <sub>odor</sub>	<b>4,800 <math>\mu\text{g}/\text{m}^3</math> (2,100 ppb)</b> <b>Short-Term ESL for Air Permit Reviews</b>	50% detection threshold, gas-house odor (i.e., slight olefinic odor, slightly aromatic odor)
<sup>acute</sup> ESL <sub>veg</sub>	- - -	Insufficient data
<b>Long-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> <sup>chronic</sup> ESL <sub>linear(nc)</sub>	<b>Long-Term ESL for Air Permit Reviews <sup>b</sup></b> <b>480 <math>\mu\text{g}/\text{m}^3</math> (210 ppb)</b>	<b>Critical Effect(s):</b> Decreased body weight in Wistar rats observed in a subacute reproductive/developmental study
<sup>chronic</sup> ESL <sub>nonthreshold(c)</sub> <sup>chronic</sup> ESL <sub>threshold(c)</sub>	- - -	No data found
<sup>chronic</sup> ESL <sub>veg</sub>	- - -	No data found

<sup>a</sup> Based on the acute ReV of 34,000  $\mu\text{g}/\text{m}^3$  (15,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

<sup>b</sup> Based on the chronic ReV of 1,600  $\mu\text{g}/\text{m}^3$  (690 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	Value	Value	Reference
Name of Chemical	2-Butene (cis and trans) *	cis-2-Butene	trans-2-Butene	OECD 2004
Molecular Formula	CH <sub>3</sub> HC=CH CH <sub>3</sub>	CH <sub>3</sub> HC=CH CH <sub>3</sub>	CH <sub>3</sub> HC=CH CH <sub>3</sub>	chemIDplus Lite
Chemical Structure				chemIDplus Lite
Molecular Weight	56.11	56.11	56.11	TRRP 2006
Physical State at 25°C	Gas	Gas	Gas	TRRP 2006
Color	Colorless	Colorless	Colorless	OECD 2004
Odor	Gas-house	Gas-house	Gas-house	Katz and Talbert 1930
CAS Registry Number	107-1-7	590-18-1	624-64-6	OECD 2004
Synonyms	Pseudobutylene; Pseudobutene; beta- Butylene; Butene, mixed -1- and -2- isomers; 1,2- Dimethylethylene; 2- Butylene; Butylene- 2; Butylene, -2	cis-beta-Butylene; 2-Butene-cis; cis- Butene; cis- Dimethylethylene; cis-1,2- Dimethylethylene; cis-2-Butylene; cis- Butylene-2; cis- Butylene, -2; (Z)- But-2-ene; 2- Butene, (2Z)-; 2- Butene, (Z)-	trans-beta-Butylene; 2-Butene-trans; trans-Butene; trans- Dimethylethylene; trans-1,2- Dimethylethylene; trans-2-Butylene; trans-Butylene-2; trans-Butylene, -2; 2-Butene, (E)-; 2- Butene, (2E)-; (E)- But-2-ene	OECD 2004
Solubility in water (mg/L)	347.58	347.58	347.58	TRRP 2006
Log K <sub>ow</sub>	2.37	2.37	2.37	TRRP 2006
Vapor Pressure (mm Hg)	1460.14	1460.14	1460.14	TRRP 2006
Relative Density (g/cm <sup>3</sup> )	0.6213 to 0.6042	0.6213	0.6042	OECD 2004
Melting Point°C	-105.5 to -138.9	-138.9	-105.5	OECD 2004
Boiling Point°C	0.8 to 3.7	3.7	0.8	OECD 2004
Conversion Factors	1 ppb = 2.29 µg/m <sup>3</sup> 1 µg/m <sup>3</sup> = 0.437 ppb	1 ppb = 2.29 µg/m <sup>3</sup> 1 µg/m <sup>3</sup> = 0.437 ppb	1 ppb = 2.29 µg/m <sup>3</sup> 1 µg/m <sup>3</sup> = 0.437 ppb	Toxicology Division

\* Usually contains cis (70%) and trans (30%) forms

## 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.

Cis- and trans-2-butene are used as solvents and cross-linking agents. They are used in the synthesis of or as a chemical intermediate for butadiene, sec-butanol, C4 and C5 derivatives, gasoline alkylate, and they are a component of liquefied petroleum gas (HSDB 2003). Estimated United States production of 2-butene was 18,990 million pounds (8,600 kilotons) in 2001 (SIAP 2004).

## Chapter 3 Acute Evaluation

### 3.1 Health-Based Acute *ReV* and *acute*ESL

Acute toxicity values were not developed separately for cis- and trans-2-butene because no studies were available on the individual isomers, although there were studies on mixtures of cis- and trans-2-butene.

#### 3.1.1 Physical/Chemical Properties and Key Studies

##### 3.1.1.1 Physical/Chemical Properties

2-Butene is a flammable, colorless gas. The log  $K_{ow}$  (2.37), moderate water solubility (347.58 milligram per liter (mg/L)) and low molecular weight (56.11) indicate the potential for 2-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 2-butene can be found in Table 3.

##### 3.1.1.2 Key and Supporting Studies

This section is based on information on 2-butene obtained from OECD (2004) as well as a search of the literature since 2000. 2-Butene appears to be somewhat more narcotic than 1-butene; the former also appears to be a mucous membrane irritant and is reported by Drantz (Patty's 1982 in OECD 2004) to be a cardiac sensitizer. The following effects as reported in ACC (2001) have been observed in mice after exposure to cis-butene (96.18% pure) for 10 minutes:

- 172,000 ppm (17.2%) induced surgical anesthesia in mice within 10 minutes (Virtue 1950 in ACC 2001)

- 255,000 ppm (25.5%) produced respiratory arrest in mice (Virtue 1950 in ACC 2001)

The following effects as reported in ACC (2001) have been observed in mice after exposure to trans-butene (98.92% pure) for 10 minutes:

- 187,000 ppm (18.7%) induced surgical anesthesia in mice within 10 minutes (Virtue 1950 in ACC 2001)
- 211,000 ppm (21.1%) produced respiratory arrest in mice (Virtue 1950 in ACC 2001)

### **3.1.1.2.1 Rat Acute Study**

In a study conducted by Arts (1992 in OECD 2004), rats were exposed for 4 hours (h) to 2-butene (approximately 50:50 mixture of cis- and trans- isomers) at a vapor concentration of 23.1 g/m<sup>3</sup> (approximately 10,000 ppm). After exposure, rats were removed from the chambers and returned to their individual living cages for 14 days of observation. Body weight was measured before study initiation and at post-exposure days 7 and 14. Rats were observed for clinical signs during exposure, shortly after exposure, and once daily during the observation period. After the observation period, rats were sacrificed, necropsied, and examined for gross pathological changes. No clinical signs were seen during the 14-day observation period. Normal growth also occurred during this period, and no abnormalities were observed at gross necropsy. The free-standing no-observed-adverse-effect-level (NOAEL) was 10,000 ppm. Arts (1992 in OECD 2004) concluded that the 4-h LC<sub>50</sub> value of 2-butene was higher than 10,000 ppm.

### **3.1.1.2.2 Rat Repeated Dose Toxicity and Reproductive/Developmental Study**

A combined repeated dose toxicity and reproductive/developmental toxicity test conducted in accordance with OECD Guideline 422 was performed by Waalkens-Brendsen and Arts (1992 in OECD 2004 and ACC 2001) and was selected as the key study. Male and female Wistar rats, 12 rats per group, were exposed to concentrations of 0, 2,500, and 5,000 ppm 2-butene (cis and trans 95% purity) via inhalation for 6 h/day; 7 days/week. Animals were exposed 2 weeks pre-mating, during mating, and during the gestation period up to and including day 19 for females. Pregnant females were exposed through gestation day (GD) 19; after which they were removed from the inhalation chambers, housed individually in the animal room, and allowed to litter normally and to rear pups to day 4 of lactation, when both dams and pups were sacrificed. Exposure of males was for the entire study (39-46 days).

A number of parameters and health effects were monitored and evaluated: observations of reaction to treatment, ill health or mortality; body weight and food consumption; hematology and clinical chemistry analyses; and microscopic examination of tissues. In addition, total litter size and number of pups of each sex, number of stillbirths, grossly malformed pups, if any, and pup body weight and organ weights were evaluated. Necropsies were performed on stillborns and pups that died during lactation. Macroscopic examinations were performed on these pups and all

pups sacrificed on day 4 post-partum and any abnormalities were recorded. All parental (F<sub>0</sub>) males and dams were examined macroscopically.

No mortality or treatment-related clinical signs were observed in F<sub>0</sub> animals. Male body weights were comparable in all groups, but mean body weight change was statistically significantly lower in the 1st and 4th week of exposure for the 2,500 ppm group and in the 1st week of exposure for the 5,000 ppm group. Female rats showed statistically significantly decreased mean body weight compared to controls at 7 and 14 days of exposure in the 5,000 ppm group and at 14 days from start of exposure in the 2,500 ppm group.

During gestation, all body weights were comparable in treated and control groups; on lactation day 1, body weight of 5,000 ppm dams was statistically significantly decreased. Body weight changes in dams were comparable to controls throughout the study. Food consumption in males was comparable to controls but food consumption by 5,000 ppm females was decreased during the first week of exposure. No other food consumption differences occurred during the study.

Mating was successful in 11/12 females in the control group and all females (12/12) in each treated group; precoital times were comparable. Female fecundity index was 73% (8/12), 75% (9/12), and 83% (10/12) in control, 2,500 ppm, and 5,000 ppm groups, respectively. Duration of pregnancy was comparable in all groups. One high dose female delivered 1 stillborn pup and 12 live pups while all other dams in all groups delivered live pups. Gestation and live birth indices were approximately 100% in all groups. No treatment-related increase in pre-implantation loss occurred. Post-implantation loss was slightly increased in the 5,000 ppm group but was within historical control limits, and the number of implantation sites in the control group was low. Total number of live births in exposed groups was slightly higher than controls. In the control and 2,500 ppm groups, one pup died between days 1 and 4 of lactation. Viability index was 97-100% and sex ratio of pups was similar in all groups. Mean body weights of pups were slightly but not statistically significantly lower in the 2,500 and 5,000 ppm groups. This might be explained by the higher number of pups in these groups compared to controls. No treatment related effects were noted in pups during lactation or at necropsy.

In conclusion, exposure to 2-butene at concentrations up to 5,000 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 (Waalkens-Brendsen and Arts, 1992 in OECD 2004).

For the first week of exposure, the shortest time period reported in the study, minimal body weight effects in female rats indicate 2,500 ppm was the NOAEL and 5,000 ppm was the lowest observed adverse effect level (LOAEL). There were decreases in mean body weight change in male rats at 2,500 ppm during the 1<sup>st</sup> week of exposure, but since male body weight was comparable to the control group, this effect in males was not considered adverse.

Concentrations of 2-butene were determined with a total carbon analyzer using flame ionization detection chromatography, twice/h in each test atmosphere. Mean actual concentrations of 2-

butene in test atmospheres were 0, 2,476 ± 68 ppm, and 5,009 ± 88 ppm. The mean analytical concentration of 2,476 ppm is used as the NOAEL.

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

Adverse effects occurring at the lowest concentration are decreases in mean body weight in female rats. The mode of action (MOA) for these effects is unknown. However, adverse acute effects for 2-butene may be related to narcotic effects. 2-Butene appears to be somewhat more narcotic than 1-butene and appears to be a mucous membrane irritant. In addition, 2-butene is reported by Drantz (Patty's 1982 in OECD 2004) to be a cardiac sensitizer.

Concentration and duration appear to play a role in 2-butene effects since exposure to 5,000 ppm produced decreased mean body weight at 7 and 14 days of exposure, whereas exposure to 2,500 ppm produced decreased mean body weight at 14 days.

In the toxicity 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 health effect that occurs at the earliest time period in the subacute study is a decrease in mean body weight in female rats after the 1<sup>st</sup> week of exposure (i.e., 7 days). The NOAEL was 2,476 ppm, since female rats showed statistically significantly decreased mean body weight at 7 and 14 days of exposure in the 5,009 ppm group. The rat study conducted by Arts (1992 in OECD 2004) was not used as the key study, because animals were only exposed to one concentration and information on how the study was conducted was not available.

#### ***3.1.3.1 Default Exposure Duration Adjustments***

The 6-h exposure duration ( $C_1$ ) was adjusted to a  $POD_{ADJ}$  of 1-h exposure duration ( $C_2$ ) using Haber's Rule as modified by ten Berge (1986) ( $C_1^n \times T_1 = C_2^n \times T_2$ ) with  $n = 3$ , where both concentration and duration play a role in toxicity:

$$\begin{aligned}POD_{ADJ} = C_2 &= [(C_1)^3 \times (T_1 / T_2)]^{1/3} \\ &= [(2,476 \text{ ppm})^3 \times (6 \text{ h} / 1 \text{ h})]^{1/3} \\ &= 4,499 \text{ ppm}\end{aligned}$$

#### ***3.1.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure***

2-Butene causes mild body weight changes which are likely to be 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). 2-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 2-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).

$$\begin{aligned} POD_{HEC} &= POD_{ADJ} \times RGDR \\ &= 4,499 \text{ ppm} \times 1 = 4,499 \text{ ppm} \end{aligned}$$

### 3.1.4 Adjustments of the $POD_{HEC}$

Since the MOA by which 2-butene produces toxicity is not understood, the default for noncarcinogenic effects is to determine a POD and apply uncertainty factors (UFs) to derive a Reference Value (ReV) (i.e., assume a threshold/nonlinear MOA). The following UFs were applied to the  $POD_{HEC}$  of 4,499 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 is no data that indicate that a  $UF_H$  larger than 10 is needed to protect children or other sensitive sub groups.
- 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 toxicity data is available for only one species. The quality of the rat study is high and the confidence in the acute database is medium.

$$\begin{aligned} \text{acute ReV} &= POD_{ADJ} / (UF_H \times UF_A \times UF_D) \\ &= 4,499 \text{ ppm} / (10 \times 3 \times 10) \\ &= 15.00 \text{ ppm} \\ &= 15,000 \text{ ppb} \end{aligned}$$

### 3.1.5 Health-Based Acute ReV and <sup>acute</sup>ESL

The acute ReV value was rounded to two significant figures. The resulting 1-h acute ReV is 15,000 ppb (34,000  $\mu\text{g}/\text{m}^3$ ). The rounded acute ReV was then used to calculate the <sup>acute</sup>ESL. At the target hazard quotient (HQ) of 0.3, the <sup>acute</sup>ESL is 4,500 ppb (10,000  $\mu\text{g}/\text{m}^3$ ) (Table 4).

**Table 4. Derivation of the Acute ReV and <sup>acute</sup>ESL**

Parameter	Summary
Study	OECD Guideline 422 combined repeated-exposure, reproduction and screening study (Waalkens-Brendsen and Arts 1992 in OECD 2004)
Study population	Male and female Wistar rats (12/sex/concentration)
Study quality	High
Exposure methods	Exposures via inhalation at 0, 2,500 and 5,000 ppm (0, 2,476 $\pm$ 68 ppm, and 5,009 $\pm$ 88 ppm analytical)
Critical effects	NOAEL based on decreased body weight in female rats after 7 days of exposure
POD	2,476 ppm (NOAEL)
Exposure duration	6 h/day for 7 days
Extrapolation to 1 h	6 h to 1 h (TCEQ 2012 with n = 3)
POD <sub>ADJ</sub> (1 h)	4,499 ppm
POD <sub>HEC</sub>	4,499 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
LOAEL UF	Not applicable
<i>Incomplete Database UF</i>	10
<i>Database Quality</i>	Medium
<b>acute ReV [1 h] (HQ = 1)</b>	<b>34,000 <math>\mu\text{g}/\text{m}^3</math> (15,000 ppb)</b>
<b><sup>acute</sup>ESL [1 h] (HQ = 0.3)</b>	<b>10,000 <math>\mu\text{g}/\text{m}^3</math> (4,500 ppb)</b>

### **3.2. Welfare-Based Acute ESLs**

#### **3.2.1 Odor Perception**

Katz and Talbert (1930 as reported in van Gemert 2003) reported 2-butene to have a “gas-house” odor (i.e., slight olefinic odor, slightly aromatic odor). The 50% odor detection threshold is  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb) (Katz and Talbert 1930 in van Gemert 2003). Katz and Talbert (1930) meet the criteria for acceptable odor threshold measurement techniques developed by the American Industrial Hygiene Association and is a Level 3 odor source TCEQ (2012), so the  $^{\text{acute}}\text{ESL}_{\text{odor}}$  for 2-butene is  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb). Since odor is a concentration-dependent effect, the same 1-h  $^{\text{acute}}\text{ESL}_{\text{odor}}$  is assigned to all averaging times.

Information on 50% odor detection thresholds for cis- and trans-2-butene individually from an approved odor source is not available, although Mullins (1955 in van Gemert 2003) reported a recognition odor threshold of  $28.5 \text{ mg}/\text{m}^3$  for cis-2-butene and  $2,700 \text{ mg}/\text{m}^3$  for trans-2-butene. The  $^{\text{acute}}\text{ESL}_{\text{odor}}$  of  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb) for 2-butene, a mixture of cis- and trans-2-butene, will be used for both the cis- and trans-2-butene isomers.

#### **3.2.2 Vegetation Effects**

Haagen-Smit et al. (1952) conducted a screening study on the effects of cis- and trans-2-butene on spinach (*Spinacia oleracea*), endive (*Cichorium endivia*), beets (*Beta vulgaris*), oats (*Avena sativa*), and alfalfa (*Medicago sativa*). Fumigations in this study were conducted at cis- or trans-butene concentrations of 4 ppm in combination with an “ozone-like” mixture of 0.24 ppm aldehyde, 0.04 ppm acid, and 0.13 ppm peroxide (calculated as  $\text{O}_3$ ) for an exposure duration of 5 h. No damage was observed as a result of exposure to 4 ppm cis-2-butene and an “ozone-like” mixture. No damage was observed as a result of exposure to 4 ppm trans-2-butene and an “ozone-like” mixture. Since the NOAELs for vegetative effects were above odor-based concentrations and the Haagen-Smit et al (1952) study did not identify a threshold effect level or treat plants with pure cis- and trans-2-butene, an  $^{\text{acute}}\text{ESL}_{\text{veg}}$  was not developed (TCEQ 2012).

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

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

- acute ReV =  $34,000 \mu\text{g}/\text{m}^3$  (15,000 ppb)
- $^{\text{acute}}\text{ESL}$  =  $10,000 \mu\text{g}/\text{m}^3$  (4,500 ppb)
- $^{\text{acute}}\text{ESL}_{\text{odor}}$  =  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb)

The short-term ESL for air permit evaluations is the  $^{\text{acute}}\text{ESL}_{\text{odor}}$  of  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb) as it is lower than the  $^{\text{acute}}\text{ESL}$  of  $10,000 \mu\text{g}/\text{m}^3$  (4,500 ppb) (Table 2). For the evaluation of ambient air monitoring data, the  $^{\text{acute}}\text{ESL}_{\text{odor}}$  of  $4,800 \mu\text{g}/\text{m}^3$  (2,100 ppb) is lower than the acute ReV of  $34,000 \mu\text{g}/\text{m}^3$  (15,000 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.

### ***3.4. Acute Inhalation Observed Adverse Effect Level***

The LOAEL of 5,009 ppm from the rat study conducted by Waalkens-Brendsen and Arts (1992 in OECD 2004) that evaluated decreased body weight in female rats was used as the initial POD for calculation of an acute inhalation observed adverse effect level. No duration adjustment was made (TCEQ 2012). The LOAEL<sub>HEC</sub> would be 5,009 ppm (Section 3.1.3.2, gas with systemic effects, based on default RGDR = 1.0)

The LOAEL<sub>HEC</sub> determined from animal studies represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The acute inhalation observed adverse effect level of 5,000 ppm (rounded to two significant figures) is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the acute inhalation observed adverse effect level of 5,000 ppm to the acute ReV of 15 ppm is a factor of 330.

## **Chapter 4 Chronic Evaluation**

### ***4.1 Noncarcinogenic Potential***

Chronic toxicity values were not developed separately for cis- and trans-2-butene because no studies were available on the individual isomers, although there were studies on mixtures of cis- and trans-2-butene.

#### **4.1.1 Physical/Chemical Properties**

Physical/chemical properties for 2-butene are discussed in Chapter 3. Since the log K<sub>ow</sub> for 2-butene is 2.37, significant bioaccumulation of 2-butene is not expected (an increase in the potential to bioconcentrate in organisms is associated with an increase in log K<sub>ow</sub> ≥ 4 (TCEQ 2012)).

#### **4.1.2 Key Study**

No subchronic or chronic toxicity studies were available describing the potential chronic toxicity of 2-butene. However, a combined repeated dose toxicity and reproductive/developmental toxicity test conducted in accordance with OECD Guideline 422 was performed by Waalkens-Brendsen and Arts (1992 in OECD 2004 and ACC 2001). This study is described in Section 3.1.1.2.2 *Rat Repeated Dose Toxicity and Reproductive/Developmental Study*. This subacute study was selected to develop a chronic ReV for 2-butene since significant bioaccumulation of 2-butene is not expected and health effects observed in the subacute study may be representative of chronic effects. Chronic exposure to 2-butene may cause an accumulation of effect, even if significant bioaccumulation does not occur.

The main findings from the Waalkens-Brendsen and Arts study (1992 in OECD 2004 and ACC 2001) was exposure to 2-butene at concentrations up to 5,000 ppm did not induce significant systemic toxicity in male rats exposed for 39-46 days, nor in pregnant female rats exposed for two weeks pre-mating, and through mating and gestation to day 19 (Waalkens-Brendsen and Arts, 1992 in OECD 2004). No developmental effects were noted. Body weight loss was the critical effect observed at the highest concentration. Mean actual concentrations of 2-butene in test atmospheres were 0, 2,476 ± 68 ppm, and 5,009 ± 88 ppm. The mean analytical concentration of 5,009 ppm is the LOAEL and 2,476 ppm is the NOAEL.

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

As mentioned previously in Section 3.1.2, the mode of action (MOA) for a decrease in body weight is unknown. The MOA for chronic health effects for 2-butene may be related to the metabolism of alkenes to epoxides. For 1-alkenes, the presence of the double bond makes these compounds optimal substrates for the cytochrome P450 enzymes that convert them to the respective epoxides that possess alkylating capacity towards nucleophilic sites in proteins and DNA. However, information on the metabolism of 2-butene is unknown. Fabiani et al. (2012) investigated the reactivity for different epoxides for 1,3-butadiene, isoprene, styrene, propylene and 1-butene *in vitro* using the comet assay in human peripheral blood mononuclear cells and promyelocytic leukaemia cells. He showed that 1-butene had a low capacity for binding to proteins and DNA when compared to the other investigated chemical. Epoxides may be rapidly metabolized by epoxide hydrolase (EH) and glutathione-S-transferase (GST) and detoxified.

In the toxicity 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 health effect that occurs in the subacute study (Waalkens-Brendsen and Arts 1992) is decrease in mean body weight in female rats. The NOAEL was 2,476 ppm.

#### 4.1.4.1 Default Exposure Duration Adjustments

Because the Waalkens-Brendsen and Arts (1992) study was a discontinuous exposure animal study (6 h/day; 7 days/week), it is necessary to adjust the animal exposure regimen to a continuous exposure.

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

where:

POD = POD from animal study based on discontinuous exposure regimen

D = exposure duration (hours per day)

$F$  = exposure frequency (days per week)

$$POD_{ADJ} = 2,476 \text{ ppm} \times (6/24 \text{ h}) \times (7/7 \text{ days})$$

$$POD_{ADJ} = 619 \text{ ppm}$$

#### 4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The physical/chemical parameters of 2-butene indicate the potential to be absorbed via the lungs and widely distributed throughout the body (Section 3.1.1.1). 2-Butene causes body weight changes which are likely to be systemic rather than point-of-entry respiratory effects. 2-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 2-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).

$$\begin{aligned} POD_{HEC} &= POD_{ADJ} \times RGDR \\ &= 619 \text{ ppm} \times 1 = 619 \text{ ppm} \end{aligned}$$

#### 4.1.5 Adjustments of the $POD_{HEC}$

Since the MOA by which 2-butene produces toxicity is not understood, the default for noncarcinogenic effects is to determine a POD and apply uncertainty factors (UFs) to derive a Reference Value (ReV) (i.e., assume a threshold/nonlinear MOA). The following UFs were applied to the  $POD_{HEC}$  of 619 ppm: 10 for intraspecies variability ( $UF_H$ ), 3 for extrapolation from animals to humans ( $UF_A$ ), 3 for use of a subacute study to develop a chronic value ( $UF_{Sub}$ ), and 10 for database uncertainty ( $UF_D$ ), for a total  $UF = 900$ :

$$\begin{aligned} \text{acute ReV} &= POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D) \\ &= 619 \text{ ppm} / (10 \times 3 \times 3 \times 10) \\ &= 0.688 \text{ ppm} \\ &= 688 \text{ ppb} \end{aligned}$$

- 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 because a subacute study was used to develop the chronic ReV and chronic exposure to 2-butene may cause an accumulation of effect. A larger  $UF_{Sub}$  was not used because 2-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 $^{chronic}ESL_{threshold(nc)}$**

The chronic ReV value was rounded to two significant figures. The resulting chronic ReV is 690 ppb ( $1,600 \mu\text{g}/\text{m}^3$ ). 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 210 ppb ( $480 \mu\text{g}/\text{m}^3$ ) (Table 5).

**Table 5. Derivation of the Chronic ReV and <sup>chronic</sup>ESL<sub>threshold(nc)</sub>**

Parameter	Summary
Study	OECD Guideline 422 combined repeated-exposure, reproduction and screening study (Waalkens-Brendsen and Arts 1992 in OECD 2004)
Study population	Male and female Wistar rats (12/sex/concentration)
Study quality	High
Exposure methods	Exposures via inhalation at 0, 2,500 and 5,000 ppm (0, 2,476 ± 68 ppm, and 5,009 ± 88 ppm analytical)
Critical effects	NOAEL based on decreased body weight in female rats
POD	2,476 ppm (NOAEL)
Exposure duration	6 h/day for 7 days
POD <sub>ADJ</sub> to continuous exposure	619
POD <sub>HEC</sub>	619 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
LOAEL UF	Not applicable
<i>Subchronic UF</i>	3
<i>Incomplete Database UF</i>	10
<i>Database Quality</i>	low
<b>chronic ReV (HQ = 1)</b>	<b>1,600 µg/m<sup>3</sup> (690 ppb)</b>
<b><sup>chronic</sup>ESL<sub>threshold(nc)</sub> (HQ = 0.3)</b>	<b>480 µg/m<sup>3</sup> (210 ppb)</b>

## 4.2 Carcinogenic Potential

There are no human or animal studies indicating that 2-butene has carcinogenic potential, so a chronic carcinogenic value was not developed. No *in vivo* genetic toxicity studies have been conducted with 2-butene. However, *in vitro* assays with 2-butene have indicated that 2-butene is non-mutagenic and non-clastogenic:

- *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation. 2-Butene was found to be non-mutagenic (Thompson 1992 in OECD 2004).
- Mutagenic assays in *E. coli* or in any of the Ames strains tested with or without metabolic activation (Araki et al. 1994 in OECD 2004). 2-Butene was found to be non-mutagenic.
- A chromosome aberration study in accordance with OECD guideline 473 and EC Directive 84/449/EEC, B10 using rat lymphocytes with and without S9 metabolic activation mix. 2-Butene-induced steep dose-related decreases in mitotic indices  $\pm$  S9; especially toxic to lymphocytes at 80% in +S9 20 h harvest group. However, 2-butene did not induce significant dose-related increases in frequency of structural chromosome aberrations or polyploid cells at any concentration level at any harvest period  $\pm$  S9. 2-Butene was not clastogenic to rat lymphocytes *in vitro* (Wright 1992 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 = 1,600  $\mu\text{g}/\text{m}^3$  (690 ppb)
- $^{\text{chronic}}\text{ESL}_{\text{threshold(nc)}} = 480 \mu\text{g}/\text{m}^3$  (210 ppb)

For the evaluation of ambient air monitoring data, the chronic ReV of 1,600  $\mu\text{g}/\text{m}^3$  (690 ppb) is used (Table 1). The long-term ESL for air permit evaluations is the  $^{\text{chronic}}\text{ESL}_{\text{threshold(nc)}}$  of 480  $\mu\text{g}/\text{m}^3$  (210 ppb) (Table 2). The  $^{\text{chronic}}\text{ESL}_{\text{threshold(nc)}}$  (HQ = 0.3) is not used for evaluation of air monitoring data (TCEQ 2012).

#### **4.5 Chronic Inhalation Observed Adverse Effect Level**

2-Butene has limited chronic toxicity data so a chronic inhalation observed adverse effect level was not determined.

## **Chapter 5. References**

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