



Development Support Document  
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# Isobutene

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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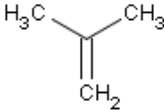
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## Chapter 1 Summary Tables

Table 1 provides a summary of health- and welfare-based values resulting from an acute and chronic evaluation of isobutene. Table 2 provides summary information on isobutene's physical/chemical properties.

<b>Table 1. Health- and Welfare-Based Values</b>		
<b>Short-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
<sup>acute</sup> ESL [1 h] (HQ = 0.3)	320,000 µg/m <sup>3</sup> (140,000 ppb)	<b>Critical Effect:</b> Based on free-standing NOAEL, no adverse effects observed in Wistar rats in a reproductive/ developmental study
Acute ReV (HQ = 1)	1,100,000 µg/m <sup>3</sup> (480,000 ppb)	
<sup>acute</sup> ESL <sub>odor</sub>	3,000 µg/m <sup>3</sup> (1,300 ppb) <b>Short-Term ESL for Air Permit Reviews</b>	50% detection threshold, gas-house odor
<sup>acute</sup> ESL <sub>veg</sub>	---	No data found
<b>Long-Term Values</b>	<b>Concentration</b>	<b>Notes</b>
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> (HQ = 0.3)	32,000 µg/m <sup>3</sup> (14,000 ppb) <b>Long-Term ESL for Air Permit Reviews</b>	<b>Critical Effect:</b> Based on free-standing NOAEL, no adverse effects observed in F344/N rats and B6C3F1 mice
Chronic ReV (HQ = 1)	110,000 µg/m <sup>3</sup> (47,000 ppb)	
<sup>chronic</sup> ESL <sub>linear(c)</sub> <sup>chronic</sup> ESL <sub>nonlinear(c)</sub>	---	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
<sup>chronic</sup> ESL <sub>veg</sub>	---	No data found

Abbreviations used: **HQ**, hazard quotient; **ppb**, parts per billion; **µg/m<sup>3</sup>**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **ReV**, Reference Value; <sup>acute</sup>**ESL**, acute health-based ESL; <sup>acute</sup>**ESL<sub>odor</sub>**, acute odor-based ESL; <sup>acute</sup>**ESL<sub>veg</sub>**, acute vegetation-based ESL; <sup>chronic</sup>**ESL<sub>nonlinear(nc)</sub>**, chronic health-based ESL for nonlinear dose-response noncancer effects; <sup>chronic</sup>**ESL<sub>linear(nc)</sub>**, chronic health-based ESL for linear dose-response noncancer effects; <sup>chronic</sup>**ESL<sub>linear(c)</sub>**, chronic health-based ESL for linear dose-response cancer effect; <sup>chronic</sup>**ESL<sub>nonlinear(c)</sub>**, chronic health-based ESL for nonlinear dose-response cancer effect and <sup>chronic</sup>**ESL<sub>veg</sub>**, chronic vegetation-based ESL; **NOAEL**, no-observed-adverse-effect level

<b>Table 2. Chemical and Physical Data</b>		
<b>Parameter</b>	<b>Value</b>	<b>Reference</b>
Molecular Formula	CH <sub>2</sub> =C(-CH <sub>3</sub> ) <sub>2</sub>	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	Katz and Talbert 1930
CAS Registry Number	115-11-7	TRRP 2006
Synonyms	2-Methyl-1-propene; 2-Methylpropylene; 2-Methylpropene; 1,1-Dimethylethene; 1,1-Dimethylethylene; Propene, 2-methyl; Isopropylidenemethylene; γ-Butylene; 2-Methyl-1-Propen; 2-Methyl-Propen; 2-Methylpropeen; 2-Methylpropen; 2-Metilpropene; 2-Metilpropeno; 2-Metyylipropeeni; α-Butylen; Butene; Butylen; Butylene; Isobuten; Isobutylen; γ-Butylen; γ-Butylene	OECD 2004
Solubility in water	238.56 mg/L	TRRP 2006
Log K <sub>ow</sub>	2.47	TRRP 2006
Vapor Pressure	1747.30 mm Hg	TRRP 2006
Relative Density	0.588 g/cm <sup>3</sup>	OECD 2004
Melting Point	-140.4°C	OECD 2004
Boiling Point	-6.9°C	OECD 2004
Conversion Factors	1 ppb = 2.29 µg/m <sup>3</sup> 1 µg/m <sup>3</sup> = 0.437 ppb	Toxicology Section

## 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.

Isobutene is only used as a chemical intermediate. It is mainly used as a monomer or copolymer for the production of synthetic rubber and various plastics. Approximately 72% is used for the production of antioxidants for food, food packaging, supplements and for plastics. Approximately 9% is used for the production of (polymer) fuel oil or lube oil additives. Approximately 2% is used for various other intermediate applications.

Estimated United States production of isobutene was 18,250 million pounds (8,300 kilotons) in 2001 (SIAP 2004).

## Chapter 3 Acute Evaluation

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

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

##### 3.1.1.1 Physical/Chemical Properties

Isobutene is a flammable, colorless gas. The log  $K_{ow}$  (2.47), low water solubility (238.56 milligram per liter (mg/L)) and low molecular weight (56.11) indicate the potential for isobutene 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 isobutene can be found in Table 2.

##### 3.1.1.2 Key Studies

This section is based on information on isobutene obtained from OECD (2004) and Cornet and Rogiers (1997) as well as a search of the literature since 2000. There are no published epidemiology studies or reports of health effects in humans after exposure to isobutene. In animals, the main effects produced after exposure to high concentrations of isobutene are narcosis, anesthesia, respiratory arrest, and/or asphyxiation (Virtue 1950 in OECD 2004 and Shugaev 1969).

- 198,000 ppm (19.8%) induced anesthesia in mice within 10 minutes (Virtue 1950 in OECD 2004)
- 320,000 ppm (32%) produced respiratory arrest in mice (Virtue 1950 in OECD 2004)
- 270,000 ppm induced a state of deep "narcosis" that was likely anesthesia in rats within 1-hour (h) (Shugaev 1969)

### 3.1.1.2.1 Acute Toxicity Studies

Mice and rats were exposed to varying concentrations of isobutene vapors in order to determine the LC<sub>50</sub> for each species. In these studies, the 2-h LC<sub>50</sub> of isobutene in mice was 180,000 ppm and the 4-h LC<sub>50</sub> in rats was 270,000 ppm (Shugaev 1969).

### 3.1.1.2.2 Reproductive/Developmental Study

A prenatal developmental inhalation toxicity study was conducted by the Central Toxicology Laboratory (CTL 2002 in OECD 2004) to OECD TG 414 guidelines under good laboratory procedures (GLP) conditions. Twenty-four mated female Wistar rats per test group were whole-body exposed to dynamically generated atmospheres of isobutene for 6 h/day on gestational days (GD) 5-21 (16 days). The target concentrations were 0, 500, 2,000 and 8,000 ppm. Chamber concentrations were determined analytically using a gas chromatographic method. The following parameters were evaluated for the pregnant dams: general state of health; clinical observation before, during, and after exposure; food and water consumption; body weight of the animals; and macroscopic findings in tissues examined post mortem. Exposure to isobutene on GD 5-21 did not elicit any maternal effects.

There were no effects of isobutene on the number, growth, or survival of the fetuses *in utero*, as evaluated by gross pathology, number of implantations, macroscopic analyses, skeletal abnormalities, minor external/visceral defects, etc. For a detailed discussion of this study, refer to OECD (2004). Thus, isobutene at exposure concentrations of up to 8,000 ppm did not have any adverse effects on fetal development.

### 3.1.1.2.3 Subchronic Repeated Exposure Study

This study is included in the acute evaluation because the reproductive/developmental study that is used as the key study was only conducted in rats and did not evaluate all the endpoints evaluated in the subchronic study. The NTP (1998) conducted a 14-week repeated exposure study in male and female F344/N rats and B6C3F<sub>1</sub> mice. Animals were exposed to 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm for 6 h/day, 5 days/week for 14 weeks. A full range of endpoints was evaluated: clinical pathology, hematology, clinical chemistry, organ weights, histopathology, sperm motility and vaginal cytology. The free-standing no observed adverse effect level (NOAEL) was 8,000 ppm. The free-standing NOAEL from both the reproductive/developmental study and the 14-week repeated exposure study were identical.

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

Effects occurring at high concentrations are anesthesia and narcosis (i.e., CNS effects). The mode of action (MOA) for CNS effects has not been clearly established, but Shugaev (1969) demonstrated that at high isobutene concentrations, there was a correlation between the narcotic properties and the accumulation of isobutene in the brains of rats. High concentrations in the brain may cause solvent effects on lipid and fatty acid compositions of membranes. The CNS effects observed in rats and mice suggest that concentration and duration play a role in CNS effects produced by isobutene.

In the reproductive/developmental 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 8,000 ppm reported from a subacute reproductive/developmental study (CTL 2002 in OECD 2004) is used as the animal POD.

#### 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:

$$\begin{aligned}POD_{ADJ} = C_2 &= [(C_1)^3 \times (T_1 / T_2)]^{1/3} \\ &= [(8,000 \text{ ppm})^3 \times (6 \text{ h} / 1 \text{ h})]^{1/3} \\ &= 14,540 \text{ ppm}\end{aligned}$$

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

Isobutene causes CNS effects, which are systemic rather than point-of-entry respiratory effects. In addition, the physical/chemical parameters of isobutene indicate the potential for isobutene to be absorbed via the lungs and widely distributed within the body (Section 3.1.1.1). Isobutene 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:

$$\begin{aligned}H_{b/g} &= \text{ratio of the blood:gas partition coefficient} \\ A &= \text{animal} \\ H &= \text{human}\end{aligned}$$

For isobutene, 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).

$$\begin{aligned}POD_{HEC} &= POD_{ADJ} \times RGDR \\ &= 14,540 \text{ ppm} \times 1 \\ &= 14,540 \text{ ppm}\end{aligned}$$

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

Since the MOA by which isobutene 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 nonlinear MOA). The following UFs were applied to the POD of 14,540 ppm: 10 for intraspecies variability ( $UF_H$ ), 3 for extrapolation from animals to humans ( $UF_A$ ), and 1 for database uncertainty ( $UF_D$ ), for a total  $UF = 30$ :

$$\begin{aligned} \text{acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_A \times \text{UF}_D) \\ &= 14,540 \text{ ppm} / (10 \times 3 \times 1) \\ &= 484.7 \text{ ppm} \\ &= 484,700 \text{ ppb} \end{aligned}$$

A  $\text{UF}_H$  of 10 was used to account for variation in sensitivity among the members of the human population. A  $\text{UF}_A$  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  $\text{UF}_D$  of 1 was used because toxicity data from a reproductive/developmental study in rats as well as a 14-week study and a chronic study investigating a wide range of endpoints is available in both rats and mice (NTP 1998). The free-standing NOAEL from each of these studies is 8,000 ppm and supports the acute study NOAEL. The confidence in the acute database is high.

### 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 480 ppm (1100  $\text{mg}/\text{m}^3$ ) or 480,000 ppb (1,100,000  $\mu\text{g}/\text{m}^3$ ). 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 140 ppm (320  $\text{mg}/\text{m}^3$ ) or 140,000 ppb (320,000  $\mu\text{g}/\text{m}^3$ ) (Table 3). The acute ReV and <sup>acute</sup>ESL are believed to be conservative since a free-standing NOAEL from a subacute study was used.

### 3.1.6 Comparison of <sup>acute</sup>ESL to Generic ESL

When a subacute study is used to derive a 1-h <sup>acute</sup>ESL, Section 3.2.3 of the ESL guidelines (TCEQ 2006) suggests a generic ESL be derived using approaches in Section 3.6 for comparison to ensure the derived value is not overly conservative. The Threshold of Concern (TOC) approach utilizes the lowest reported inhaled concentrations at which fifty percent of the study specimens die after exposure ( $\text{LC}_{50}$ ). Shugaev (1969) reported the 2-h  $\text{LC}_{50}$  of isobutene in mice was 180,000 ppm and the 4-h  $\text{LC}_{50}$  in rats was 270,000 ppm which would classify isobutene as a TOC Category 5 gas and the corresponding generic ESL would be 1000  $\mu\text{g}/\text{m}^3$  (Table 3-3 of the ESL guidelines (TCEQ 2006)). Therefore, the 1-h <sup>acute</sup>ESL of 140,000 ppb (320,000  $\mu\text{g}/\text{m}^3$ ) based on the subacute study is higher than the generic ESL for a Category 5 gas. This provides confidence that the derived value is not overly conservative.

<b>Table 3. Derivation of the Acute ReV and <sup>acute</sup>ESL</b>	
Study	Key: Reproductive/developmental test (CTL 2002 in OECD 2004) Supporting: 14-week study in F344/N rats and B6C3F1 mice (NTP 1998)
Study population	Wistar female rats (24/group)
Study quality	high
Exposure methods	Exposures via inhalation at 0, 500, 2,000 and 8,000 ppm
Critical effects	Free standing NOAEL, no observed effects in pregnant dams or fetuses
POD	8,000 ppm (free standing NOAEL)
Exposure duration	6 h/day, 16 days [GD 5-21]
Extrapolation to 1 h	6 h to 1 h (TCEQ 2006 with n = 3)
POD <sub>ADJ</sub> (1 h)	14,540 ppm
POD <sub>HEC</sub>	14,540 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	30
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	Not applicable
<i>Incomplete Database UF</i>	1
<i>Database Quality</i>	high
<b>acute ReV [1 h] (HQ = 1)</b>	<b>1,100,000 µg/m<sup>3</sup> (480,000 ppb)</b>
<b><sup>acute</sup>ESL [1 h] (HQ = 0.3)</b>	<b>320,000 µg/m<sup>3</sup> (140,000 ppb)</b>

### 3.2. Welfare-Based Acute ESLs

#### 3.2.1 Odor Perception

Katz and Talbert (1930 as reported in van Gemert 2003) reported isobutene to have a “gas-house” odor and report a 50% odor detection threshold of 3,000 µg/m<sup>3</sup> (1,300 ppb). The 50% odor detection threshold for isobutene determined by the triangular odor bag method was 22,900 µg/m<sup>3</sup> (10,000 ppb) (Nagata 2003). Both Nagata (2003) and Katz and Talbert (1930) meet the criteria for acceptable odor threshold measurement techniques developed by the American Industrial Hygiene Association and USEPA as discussed in TCEQ (2006). The lowest value of 3,000 µg/m<sup>3</sup> (1,300 ppb) reported by Katz and Talbert (1930 in van Gemert 2003) is the <sup>acute</sup>ESL<sub>odor</sub>. Since odor is a concentration-dependent effect, the same 1-h <sup>acute</sup>ESL<sub>odor</sub> is assigned to all averaging times.

#### 3.2.2 Vegetation Effects

No data were found regarding short-term vegetative effects.

### ***3.3. Short-Term ESL***

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

- acute ReV = 1,100,000  $\mu\text{g}/\text{m}^3$  (480,000 ppb)
- acute<sup>c</sup>ESL = 320,000  $\mu\text{g}/\text{m}^3$  (140,000 ppb)
- acute<sup>c</sup>ESL<sub>odor</sub> = 3,000  $\mu\text{g}/\text{m}^3$  (1,300 ppb)

The short-term ESL for air permit evaluations is the acute<sup>c</sup>ESL<sub>odor</sub> of 3,000  $\mu\text{g}/\text{m}^3$  (1,300 ppb), as it is lower than the acute<sup>c</sup>ESL of 320,000  $\mu\text{g}/\text{m}^3$  (140,000 ppb) (Table 1).

## **Chapter 4 Chronic Evaluation**

This section is based on information on isobutene obtained from OECD (2004), the US National Toxicology Program (NTP 1998), and a search of the literature since 2000. There are no published epidemiology studies or reports of health effects in humans after exposure to isobutene. The US National Toxicology Program (NTP 1998) exposed F344/N rats or B6C3F1 mice (50 males and 50 females/group, 6 weeks of age) by inhalation to isobutene for 6 h/day, 5 days/week, for 105 weeks to 0, 500, 2,000 or 8,000 ppm isobutene. The NTP performed evaluations of clinical pathology, hematology, clinical chemistry, histopathology, complete necropsy and examinations of numerous organs, sperm motility and vaginal cytology. For the rat study, mean actual concentrations of isobutene in test atmospheres were  $497 \pm 21$ ,  $1,990 \pm 72$ , and  $7,940 \pm 313$  ppm. For the mouse study, mean actual concentrations of isobutene in test atmospheres were  $498 \pm 20$ ,  $1,990 \pm 74$ , and  $7,960 \pm 283$  ppm.

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

#### **4.1.1 NTP Rat Study**

The survival of exposed male and female rats was similar to that of the controls. Mean body weights of exposed groups were generally similar to those of the controls throughout the study. Isobutene exposure caused an increased incidence of thyroid gland follicular cell carcinoma in the 8,000 ppm male rat group and a marginal increase in the incidences of hyaline degeneration of the olfactory epithelium (NTP 1998). There were no exposure-related findings in any of the other parameters evaluated.

In regards to the increased incidence of thyroid gland follicular cell carcinoma, there were no concurrent increases in the incidences of thyroid gland follicular cell hyperplasia or adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the controls. Potential carcinogenic effects are discussed in greater detail in Section 4.2.

Exposure of rats to isobutene caused an increase, although marginal, in the incidences of hyaline degeneration of the olfactory epithelium of the nose in males and females. More importantly, the severities of this lesion (mild to moderate) were increased in exposed males and females in a concentration-related fashion (Table 4). In inhalation studies, hyaline degeneration is a commonly observed change in the epithelium of the nasal cavity, the incidence and severity of which may increase with increasing exposure concentration. The accumulation of these protein globules is considered a nonspecific adaptive response to prolonged inhalation of irritant material and has no adverse effect on exposed animals (NTP 1998). Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct

in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats, although no nasal neoplasms were observed in male or female rats exposed to isobutene (see Table 4).

<b>Table 4. Effects in Rats after Exposure to Isobutene</b>				
Concentration	0 ppm	500 ppm	2,000 ppm	8,000 ppm
Males - Hyaline degeneration severity <sup>1</sup>	43/49 1.3	45/49 1.4	46/50 2.2	49/49 2.6
Females - Hyaline degeneration severity <sup>1</sup>	44/50 1.5	47/50 2.4	48/50 2.8	47/49 2.8
Males - minimal hypertrophy of goblet cells	43/49	45/49	46/50	49/49
Females - minimal hypertrophy of goblet cells	44/50	47/50	48/50	47/49

<sup>1</sup> severity scale of 0 to 4

#### 4.1.2 NTP Mouse Study

In the mouse study, neither survival rates nor body weight gains in males were significantly affected by isobutene exposure. Although survival rates for female mice were not affected by exposure, female mice exposed to 2,000 or 8,000 ppm weighed slightly less than the controls in the second year of the study. The only exposure-related findings in the parameters evaluated by the NTP (1998) were non-neoplastic nasal lesions that were minimal to mild in severity. Hyaline degeneration of the respiratory epithelium occurred in all exposed groups of males and females, was significantly greater than that in control groups, and occurred with positive trends (see Table 5). The severities of this lesion (minimal to mild) were less than that observed in rats but increased in exposed males in a concentration-related fashion and in females only at 8,000 ppm. The incidence of hyaline degeneration of the olfactory epithelium in males occurred with a positive trend and was significantly greater in males exposed to 2,000 and 8,000 ppm than in controls. The incidence of hyaline degeneration of the olfactory epithelium in females also occurred with a positive trend; however, the incidences were not statistically different from controls. Although they were not observed in the 14-week mouse study, these lesions are fairly common in long-term inhalation studies, and, as discussed above, have no adverse effect on exposed animals (NTP 1998). No nasal neoplasms were observed in male or female mice.

Concentration	0 ppm	500 ppm	2,000 ppm	8,000 ppm
Males - Hyaline degeneration of respiratory epithelium severity <sup>1</sup>	6/50 1.0	19/49 1.2	29/50 1.5	39/48 1.8
Females - Hyaline degeneration of respiratory epithelium severity <sup>1</sup>	21/47 1.8	39/50 1.5	41/49 1.6	48/50 2.3
Males - Hyaline degeneration of olfactory epithelium	6/50 1.0	7/50 1.1	16/50 1.6	17/48 1.4
Females - Hyaline degeneration of olfactory epithelium	17/47 1.5	19/50 1.2	24/49 1.1	27/50 1.2

<sup>1</sup> severity scale of 0 to 4

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

The metabolism of isobutene has been recently reviewed by Cornet and Rogiers (1997). Isobutene is metabolized in the liver by the CYP2E1 cytochrome P-450 isoform to 2-methyl-1,2-epoxypropane (MEP) (1,1-dimethyloxirane), a reactive epoxide (Figure 1). The epoxide is rapidly metabolized by epoxide hydrolase (EH) and glutathione-S-transferase (GST), converting the epoxide to 2-methyl-1,2-propanediol and to a glutathione conjugate, respectively. Csanady et al. (1991 in NTP 1998) investigated the metabolism of isobutene in rats and mice and compared the amount of MEP formed to that of ethene-oxide and 1,2-epoxy-3-butene, reactive epoxides of ethene and 1,3-butadiene, respectively. Under conditions of saturation of isobutene metabolism, the concentration of MEP in the atmosphere of a closed exposure system when Sprague-Dawley rats were exposed to isobutene was only about 7% of that observed for ethene-oxide (epoxide of ethene) and about 1% of that observed for 1,2-epoxy-3-butene (epoxide of 1,3-butadiene). This may indicate that MEP is rapidly detoxified by EH and GST and does not accumulate. The balance between formation and detoxification of MEP will determine whether adverse health effects occur after exposure to isobutene (Cornet and Rogiers 1997). The rate of isobutene epoxidation appears to be significantly lower in human liver than in rodent liver, particularly in mouse liver, when evaluated in an *in vitro* system of liver tissues (Cornet et al. 1995). Although the epoxide of isobutene may play a role in its toxicity, the precise mechanism by which isobutene produces adverse health effects is not understood.

Data on exposure concentration of the parent chemical is available from the NTP (1999) study. 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), exposure concentration of the

parent chemical will be used as the default dose metric.

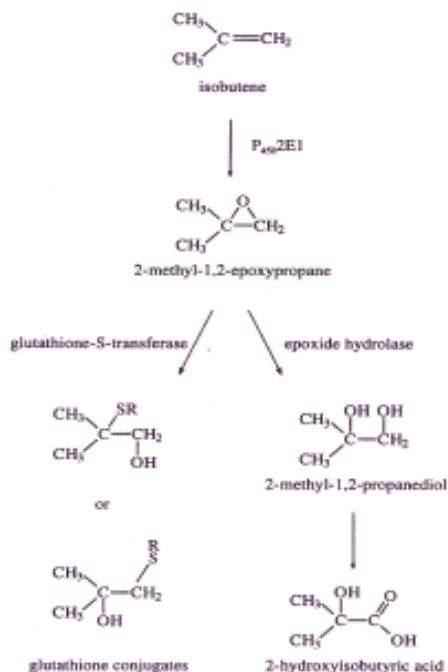


FIGURE 1  
Biotransformation of Isobutene

**Figure 1. Schematic of Isobutene Metabolism** (Figure 1 from NTP (1998))

#### 4.1.4 Point-of-Departure (POD) and Dosimetric Adjustments

The free-standing NOAEL identified in the NTP (1998) study was 8,000 ppm (7,960 ppm analytical). Hyaline degeneration in the respiratory and olfactory epithelia in rats and mice and slight weight loss in female mice in the second year of exposure were not considered adverse effects.

##### 4.1.4.1 Default Exposure Duration Adjustments

The highest free-standing NOAEL of 7,960 ppm (analytical) from the mouse study reported by the NTP (1998) was used to derive the chronic ReV. The animal POD from the NTP (1998) study was adjusted to a POD associated with a continuous exposure scenario, or  $POD_{ADJ}$ , as outlined in section 4.2.2 of the guidelines (TCEQ 2006) by using the following formula:

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

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

$$POD_{ADJ} = 7,960 \text{ ppm} \times (6/24) \times (5/7) = 1,421 \text{ ppm}$$

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

Isobutene causes CNS effects, which are systemic rather than point-of-entry respiratory effects. In addition, the physical/chemical parameters of isobutene indicate the potential for isobutene to be absorbed via the lungs and widely distributed within the body (Section 3.1.1.1). Isobutene 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 isobutene, 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).

$$\begin{aligned} POD_{HEC} &= POD_{ADJ} \times RGDR \\ &= 1,421 \text{ ppm} \times 1 \\ &= 1,421 \text{ ppm} \end{aligned}$$

#### 4.1.5 Adjustment of $POD_{HEC}$

The default for noncarcinogenic effects is to determine a POD and apply UFs to extrapolate from the POD to lower concentrations (i.e., assume a nonlinear MOA) in order to calculate a ReV.

To calculate the chronic ReV, the  $POD_{ADJ}$  was divided by appropriate UFs: a  $UF_H$  of 10 to account for variation in sensitivity among the members of the human population; 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; and a  $UF_D$  of 1 since the database for isobutene is considered to be adequate, for a total UF of 30:

$$\begin{aligned} \text{Chronic ReV} &= POD_{ADJ} / (UF_H \times UF_A \times UF_D) \\ &= 1,421 \text{ ppm} / (10 \times 3 \times 1) \\ &= 47.37 \text{ ppm} \\ &= 47,370 \text{ ppb} \end{aligned}$$

#### 4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV value was rounded to two significant figures. The resulting chronic ReV is 47,000 ppb (110,000  $\mu\text{g}/\text{m}^3$ ). The rounded chronic ReV was then used to calculate the  $^{chronic}ESL_{nonlinear(nc)}$ . At the target HQ of 0.3, the  $^{chronic}ESL_{nonlinear(nc)}$  is 14,000 ppb (32,000  $\mu\text{g}/\text{m}^3$ ) (Table 6).

<b>Table 6. Derivation of the Chronic ReV and <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub></b>	
Study	2-year bioassays (NTP 1998)
Study Population	F344/N rats or B6C3F1 mice, 50 males and 50 females/group
Study Quality	High
Exposure Method	Exposures via inhalation at 0, 500, 2,000 or 8,000 ppm [analytical concentration: (Rat 497 ± 21, 1,990 ± 72, and 7,940 ± 313 ppm) (mouse 498 ± 20, 1,990 ± 74, and 7,960 ± 283 ppm)]
Critical Effects	Free-Standing NOAEL – Hyaline degeneration in the respiratory and olfactory epithelium in rats and mice and slight weight loss in female mice in the second year of exposure were not considered adverse effects.
POD (original animal study)	7,960 ppm (free-standing NOAEL from mouse study)
Exposure Duration	6 h/day, 5 days/week for 105 weeks
Extrapolation to continuous exposure (POD <sub>ADJ</sub> )	1,421 ppm
POD <sub>HEC</sub>	1,421 ppm
Total UFs	30
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	Not applicable
<i>Subchronic to chronic UF</i>	Not applicable
<i>Incomplete Database UF</i>	1
<i>Database Quality</i>	High
<b>Chronic ReV (HQ = 1)</b>	<b>110,000 µg/m<sup>3</sup> (47,000 ppb)</b>
<b><sup>chronic</sup>ESL<sub>nonlinear(nc)</sub> (HQ = 0.3)</b>	<b>32,000 µg/m<sup>3</sup> (14,000 ppb)</b>

## 4.2 Carcinogenic Potential

There have been numerous studies to evaluate the *in vivo* and *in vitro* genotoxic capacities of isobutene and its epoxide metabolite, MEP. These studies are discussed in OECD (2004) and Cornet and Rogiers (1997). Isobutene does not appear to be mutagenic, whereas MEP was demonstrated to have mutagenic potential. However, as discussed in Section 4.1.2, MEP is rapidly detoxified by EH and GST and significantly less MEP is formed in humans than in rodents (Cornet et al. 1995).

Two-year carcinogenicity studies were conducted by the NTP (1998) in F344/N rats and B6C3F1 mice and are described in Section 4.1. There was some evidence of carcinogenic activity of isobutene in male F344/N rats based on an increased incidence of follicular cell carcinoma of the thyroid gland observed at the highest dose of 8,000 ppm. The combined incidence of C-cell adenoma and carcinomas in male rats was:

- 5/48 (controls)
- 4/48 (500 ppm)
- 7/48 (2,000 ppm) and
- 8/50 (8,000 ppm).

The incidence of follicular cell carcinoma in male rats was:

- 1/48 (controls)
- 0/48 (500 ppm)
- 0/48 (2,000 ppm) and
- 5/50 (8,000 ppm).

There was no evidence of carcinogenic activity of isobutene in female F344/N rats or male or female B6C3F1 mice. Using the suggested narrative in USEPA (2005), the TS determined that the data are inadequate for an assessment of human carcinogenic potential via the inhalation route for the following reasons:

- the histomorphology of the carcinomas in male rats was similar to the morphologic spectrum typical of spontaneously developing follicular cell carcinomas;
- there were no concurrent increases in the incidences of thyroid gland follicular cell hyperplasia or adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the controls;
- the tumors occurred only in one sex of one species;
- there were no precursor lesions, such as hyperplasia or adenoma, and the tumor type occurs spontaneously; the tumors were only singular and unilateral and did not form metastases;
- there was no increase in liver weight giving indication of a secondary mechanism; and
- the thyroid was not a target organ of isobutene toxicity in repeated dose studies (OECD 2004).

### ***4.3. Welfare-Based Chronic ESL***

No data were found regarding long-term vegetative effects.

### ***4.4 Long-Term ESL***

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

- Chronic ReV = 110,000  $\mu\text{g}/\text{m}^3$  (47,000 ppb)
- $\text{chronicESL}_{\text{nonlinear(nc)}}$  = 32,000  $\mu\text{g}/\text{m}^3$  (14,000 ppb)

The long-term ESL for air permit reviews is the  $\text{chronicESL}_{\text{nonlinear(nc)}}$  of 32,000  $\mu\text{g}/\text{m}^3$  (14,000 ppb) (Table 1). The long-term ESL of 32,000  $\mu\text{g}/\text{m}^3$  (14,000 ppb) is higher than the short-term odor-based ESL of 3,000  $\mu\text{g}/\text{m}^3$  (1,300 ppb) (Table 1). Thus, if the 1-h modeling concentrations meet the short-term ESL, no

acute or chronic adverse effects are expected to occur as a result of exposure to isobutene emissions from a permitted facility.

## Chapter 5. References

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### 5.2 Other Studies and Documents Reviewed by the TS

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