Development Support Document
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Isobutene

CAS Registry Number: 115-11-7

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on April 15, 2008.

Revised DSD March 14, 2014: The DSD was revised based on updated guidance in TCEQ (2012) (i.e., when a toxicity study only identifies a free-standing NOAEL, a duration adjustment from a longer duration to a shorter duration is not conducted).

Revised DSD September 14, 2015: An odor-based value was not developed because isobutene does not have a pungent or disagreeable odor (TCEQ 2015). Isobutene has a slight olefinic odor, slight aromatic odor.

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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
CRO	crotonaldehyde
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

Acronyms and Abbreviations	Definition
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_{50}	Inhibitory concentration at a 50% response level
IL	interleukin
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
$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number

Acronyms and Abbreviations	Definition
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
OAEL	Observed adverse effect level
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

Acronyms and Abbreviations	Definition
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of isobutene. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicty 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 isobutene's physical/chemical data.

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

Short-Term Values	Concentration	Notes
Acute ReV	**Short-Term Health** **620,000 µg/m^3 (270,000 ppb)**	**Critical Effect(s):** Based on a free-standing NOAEL, no adverse effects observed in Wistar rats in a reproductive/ developmental study
$^{acute}ESL_{odor}$	- - -	Slight olefinic odor, slight aromatic odor
$^{acute}ESL_{veg}$	- - -	Concentrations producing vegetative effects were significantly above other values
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**Long-Term Health** **110,000 µg/m^3 (47,000 ppb)**	**Critical Effect(s):** Based on a free-standing NOAEL, no adverse effects observed in F344/N rats and B6C3F1 mice after chronic exposure
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Isobutene is not monitored for by the TCEQ's ambient air monitoring program

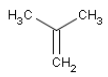
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	**Short-Term ESL for Air Permit Reviews 180,000 µg/m^3 (81,000 ppb)** [a]	**Critical Effect:** Based on a free-standing NOAEL, no adverse effects observed in Wistar rats in a reproductive/ developmental study
$^{acute}ESL_{odor}$	- - -	Slight olefinic odor, slight 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 32,000 µg/m^3 (14,000 ppb)** [b]	**Critical Effect(s):** Based on a free-standing NOAEL, no adverse effects observed in F344/N rats and B6C3F1 mice
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	No data found
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Based on the acute ReV of 620,000 µg/m^3 (270,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[b] Based on the chronic ReV of 110,000 µg/m^3 (47,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$CH_2 =C(-CH_3)_2$	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 (i.e., slight olefinic odor, slightly aromatic 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; y-Butylene; 2-Methyl-1-Propen; 2-Methyl-Propen; 2-Methylpropeen; 2-Methylpropen; 2-Metilpropene; 2-Metilpropeno; 2-Metyylipropeeni; a-Butylen; Butene; Butylen; Butylene; Isobuten; Isobutylen; y-Butylen; y-Butylene	OECD 2004
Solubility in water	238.56 mg/L	TRRP 2006
Log K_{ow}	2.47	TRRP 2006
Vapor Pressure	1747.30 mm Hg	TRRP 2006
Relative Density	0.588 g/cm^3	OECD 2004
Melting Point	-140.4°C	OECD 2004
Boiling Point	-6.9°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.
>
> 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 ^{acute}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), moderate 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 3.

3.1.1.2 Key and Supporting 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)
- 270,000 ppm (27%) induced a state of deep "narcosis" that was likely anesthesia in rats within 1-hour (h) (Shugaev 1969)
- 320,000 ppm (32%) produced respiratory arrest in mice (Virtue 1950 in OECD 2004)

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_{50} for each species. In these studies, the 2-h LC_{50} of isobutene in mice was 180,000 ppm and the 4-h LC_{50} 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 and was selected as the key study. 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$_1$ 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 Exposure Duration Adjustments

The POD obtained from the CTL (2002) 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

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).

$$POD_{HEC} = POD_{ADJ} \times RGDR$$
$$= 8{,}000 \text{ ppm} \times 1$$
$$= 8{,}000 \text{ ppm}$$

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 threshold/nonlinear MOA). The following UFs were applied to the POD of 8,000 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:

- A UF_H of 10 was used to account for variation in sensitivity among the 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 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.

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 8{,}000 \text{ ppm} / (10 \times 3 \times 1)$$
$$= 266.7 \text{ ppm}$$

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

The acute ReV was rounded to two significant figures. The resulting 1-h acute ReV is 270 ppm (620 mg/m^3) or 270,000 ppb (620,000 µg/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 81 ppm (180 mg/m^3) or 81,000 ppb (180,000 µg/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	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	No adjustment since the POD was a free-standing NOAEL (TCEQ 2012)
POD_{ADJ} (1 h)	8,000 ppm
POD_{HEC}	8,000 ppm (gas with systemic effects, based on default RGDR = 1.0)
Total uncertainty factors (UFs)	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Incomplete Database UF *Database Quality*	1 high
acute ReV [1 h] (HQ = 1)	**620,000 µg/m^3 (270,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**180,000 µg/m^3 (81,000 ppb)**

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 (i.e., slight olefinic odor, slight aromatic odor) and report a 50% odor detection threshold of 3,000 µg/m^3 (1,300 ppb). The 50% odor detection threshold for isobutene determined by the triangular odor bag method was 23,000 µg/m^3 (10,000 ppb) (Nagata 2003). Since isobutene does not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

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 = 620,000 µg/m^3 (270,000 ppb)
- $^{acute}ESL$ = 180,000 µg/m^3 (81,000 ppb)

The short-term ESL for air permit evaluations is the $^{acute}ESL$ of 180,000 µg/m^3 (81,000 ppb) (Table 2).

3.4. Acute Inhalation Observed Adverse Effect Level

Isobutene has limited toxicity data (i.e., only a free-standing NOAEL of 8,000 ppm from a subacute study was identified or higher concentrations that produced severe adverse effects) so an acute inhalation observed adverse effect level was not determined.

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 ± 21, 1,990 ± 72, and 7,940 ± 313 ppm. For the mouse study, mean actual concentrations of isobutene in test atmospheres were 498 ± 20, 1,990 ± 74, and 7,960 ± 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 5).

Table 5. Effects in Rats after Exposure to Isobutene

Concentration	0 ppm	500 ppm	2,000 ppm	8,000 ppm
Males - Hyaline degeneration severity [1]	43/49 1.3	45/49 1.4	46/50 2.2	49/49 2.6
Females - Hyaline degeneration severity [1]	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

[1] 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 6). 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.

Table 6. Effects in Mice after Exposure to Isobutene

Concentration	0 ppm	500 ppm	2,000 ppm	8,000 ppm
Males - Hyaline degeneration of respiratory epithelium severity [1]	6/50 1.0	19/49 1.2	29/50 1.5	39/48 1.8
Females - Hyaline degeneration of respiratory epithelium severity [1]	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

[1] 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.

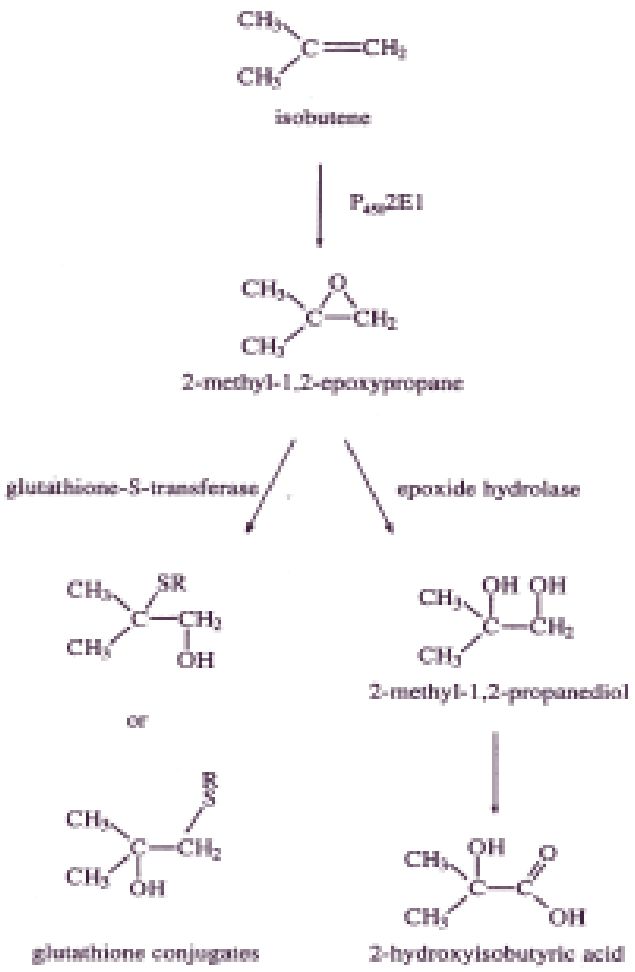


FIGURE 1
Biotransformation of Isobutene

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. Even though the POD was a free-standing NOAEL, an adjustment from a discontinuous to a continuous exposure duration was conducted (TCEQ 2012), as follows:

POD_{ADJ} = POD x (D/24 hours) x (F/7 days)

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

POD_{ADJ} = 7,960 ppm x (6/24) x (5/7) = 1,421 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).

$POD_{HEC} = POD_{ADJ} \times RGDR$

= 1,421 ppm x 1

= 1,421 ppm

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 threshold/nonlinear MOA) in order to calculate a ReV.

To calculate the chronic ReV, the POD_{ADJ} was divided by appropriate UFs, for a total UF of 30:

- A UF_H of 10 was used to account for variation in sensitivity among the 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.

- UF_D of 1 since the database for isobutene is considered to be adequate. The quality of the rat study is high and the confidence in the chronic database is medium.

Chronic ReV = POD_{ADJ} / (UF_H x UF_A x UF_D)
= 1,421 ppm / (10 x 3 x 1)
= 47.37 ppm
= 47,370 ppb

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 47,000 ppb (110,000 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target HQ of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 14,000 ppb (32,000 µg/m^3) (Table 7).

Table 7. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Summary
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_{ADJ})	1,421 ppm
POD_{HEC}	1,421 ppm
Total UFs	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Subchronic to chronic UF	Not applicable
Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**110,000 µg/m^3 (47,000 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**32,000 µg/m^3 (14,000 ppb)**

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 4.1.3, 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 decribed 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 TD 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 hypersplasia 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 µg/m^3 (47,000 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 32,000 µg/m^3 (14,000 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 32,000 µg/m^3 (14,000 ppb) (Table 2). The long-term ESL of 32,000 µg/m^3 (14,000 ppb) is higher than the short-term odor-based ESL of 23,000 µg/m^3 (10,000 ppb) (Table 2). 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.

4.5 Chronic Inhalation Observed Adverse Effect Level

A free-standing NOAEL was used to determine the chronic ReV for isobutene, so a chronic inhalation observed adverse effect level was not determined.

Chapter 5 References

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