Isoprene

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Prepared by
Tracie Phillips, Ph.D.
Joseph T. Haney, Jr., M.S.
Toxicology Division

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

DSD History

Effective Date	Reason
2006	Isoprene listed on public website as a chemical under consideration for ESL development
August 31, 2012	Report on carcinogenic dose-response modeling conducted by Sielken & Associates, Inc. provided to TCEQ
July 1, 2013	Report on Letter Peer Review for initial draft carcinogenic section of DSD conducted by TERA provided to TCEQ
October 29, 2015	TCEQ publishes “Development of an inhalation unit risk factor for isoprene” after carcinogenic section re-evaluation
November 29, 2017	DSD proposed for public comment
To be determined	DSD posted as final

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADAF	Age-dependent Default Adjustment Factor
AEGL	Acute Exposure Guideline Level
AMCV	Air monitoring comparison values
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
$BMCL_{10}$	benchmark concentration lower corresponding to the 10% response level
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	benchmark dose software
BMR	benchmark response
C	concentration
Cal EPA	California Environmental Protection Agency
CI	confidence interval
CIIT	Chemical Industry Institute of Toxicology
CNS	central nervous system
D	exposure duration, hour per day
d	day
DF	deposition fraction in the target region of the respiratory tract
DAF	dosimetric adjustment factor
DNA	deoxyribonucleic acid
DSD	development support document
E	exposure level or concentration

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Acronyms and Abbreviations	Definition
EC	effective concentration
EC_{10}	effective concentration corresponding to the 10% response level
ET	extrathoracic
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose-response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose-response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LEC	lowest effective concentration
LEC_{10}	lowest effective concentration corresponding to the 10% response level
LOAEL	lowest-observed-adverse-effect-level
MF	modifying factor
MLE	maximum likelihood estimate

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Acronyms and Abbreviations	Definition
MW	molecular weight
µg	microgram
µm	micrometer
Mm	millimeter
min	minute
MMAD	mass median aerodynamic diameter
MPPD	multiple pass particle dosimetry
MOA	mode of action
MRL	Minimal Risk Level
NA	not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NTP	National Toxicology Program
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
POE	portal of entry
ppbv	parts per billion by volume
ppm	parts per million
RDDR	regional deposited dose ratio
RD_0	the threshold concentration for reduction of the respiratory rate, corresponds to the NOEL
ReV	Reference Value
RfC	Reference Concentration
RfD	Reference Dose
SD	standard deviation
σ_g	geometric variance

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Acronyms and Abbreviations	Definition
T	time or exposure duration
TB	tracheobronchial
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TH	thoracic
TRI	Toxics Release Inventory
TWA	Time-Weighted Average
TWA-TLV	Time-Weighted Average Threshold Limit Value
UCL	upper confidence limit
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
URF	Unit Risk Factor
VE	minute ventilation
VE_{ho}	default occupational ventilation rate for an eight-hour day
VE_h	default non-occupational ventilation rate for a 24-h day
WHO	World Health Organization
WOE	weight of evidence

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Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of isoprene, respectively, for use in air permitting and air monitoring. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (2015a) for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on isoprene's physical/chemical parameters.

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Table 1. Acute Health and Welfare-Based Screening Values for Isoprene

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated / RPF	Critical Effect(s)	Notes
Acute ReV	6 h	3,900	1,400	M	A	--	Decreased female mouse fetal body weight.	Reproductive/developmental effects, duration not adjusted to 1-hour.
Acute ReV-24hr	--	--	--	--	--	--	--	--
^{acute}ESL [a]	6 h	1,200	420	P	D	--	Same as above.	--
^{acute}IOAEL	--	--	--	--	--	--	--	--
^{subacute}IOAEL	12 d	720,000	258,000	N	none	--	Same as above.	Margin of exposure between this and the 6-h acute ReV is a factor of 184.
^{acute}ESL$_{odor}$	**1 h**	**130**	**48**	**M,P**	**A,S,D**	**--**	**--**	**50% odor detection threshold.**
^{acute}ESL$_{veg}$	--	--	--	--	--	--	--	No relevant data found.

Bold values used for air permit reviews

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

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Table 2. Chronic Health and Welfare-Based Screening Values for Isoprene

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Chronic $ReV_{threshold(nc)}$	70 yr	390	140	M	A	--	Decreased forelimb and hindlimb grip strength.	--
$^{chronic}ESL_{threshold(nc)}$ [a]	**70 yr**	**120**	**42**	**P**	**S,D**	**--**	**Same as above.**	**--**
$^{chronic}IOAEL_{(nc)}$	70 yr	610	220	N	none	--	Same as above.	--
$^{chronic}ESL_{threshold(c)}$	--	--	--	--	--	--	--	--
$^{chronic}ESL_{nonthreshold(c)}$ [b]	70 yr	450	160	N	none	--	Liver carcinoma in mice.	--
$^{chronic}IOAEL_{(c)}$	6 mo	610,000	220,000	--	--	--	Decreased forelimb and hindlimb grip strength.	Margin of exposure between this and the chronic ReV is a factor of 1,570.
$^{chronic}ESL_{veg}$	--	--	--	--	--	--	--	No relevant data found

Bold values used for air permit reviews

[a] Based on the chronic ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the URF of 2.2E-08 $(\mu g/m^3)^{-1}$ or 6.2E-08 $(ppb)^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

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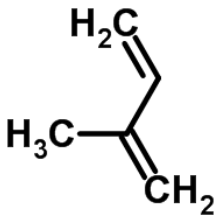
Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_5H_8	Chemfinder 2004
Chemical Structure		ChemSpider
Molecular Weight	68.12 (g/mol)	HSDB 2002
Physical State	Liquid	USDHHS 2004
Color	Colorless	USDHHS 2004
Odor	Mild aromatic	HSDB 2002
CAS Registry Number	78-79-5	Chemfinder 2004
Synonyms	2-methyl-1,3-butadiene; 2-methylbutadiene; isopentadiene	Chemfinder 2004
Solubility in water	Insoluble <0.1 g/100 mL at 21.5 °C; 642 ppm at 25 °C	Chemfinder 2004; HSDB 2002
Log K_{ow} or P_{ow}	log K_{ow} = 2.42	HSDB 2002
Vapor Pressure	550 mm Hg at 25 °C 400 mm Hg a 15.4 °C	HSDB 2002, The Merck Index 2001
Vapor Density (air = 1)	2.4	HSDB 2002
Density	0.681 g/cm^3 (at 20 °C)	HSDB 2002
Melting Point	-145.95 °C	HSDB 2002
Boiling Point	34.067 °C	HSDB 2002
Conversion Factors	1 µg/m^3 = 0.36 ppb at 25 °C 1 ppb = 2.79 µg/m^3 at 25 °C	CDC 2007; HSDB 2002

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Chapter 2 Major Uses or Sources and Ambient Air Concentrations

2.1 Major Uses or Sources

Isoprene is the 2-methyl analogue of 1,3-butadiene. It is used largely in the manufacturing of synthetic rubber. It is also used in the manufacturing of styrene-isoprene-styrene block co-polymers and butyl rubber, in the production of hydrocarbon resins, and for the synthesis of terpenes (BG Chemie 2000, Melnick et al. 1996, Sharkey 1996). Anthropogenic sources of isoprene include: petroleum cracking, ethylene production (by-product), wood pulp production, oil fires, tobacco smoke, and automobile exhaust (Hurst 2007, Melnick et al. 1996, Sharkey 1996).

Isoprene is produced naturally by plants, animals, and bacteria. The amount of isoprene produced naturally far exceeds that which is produced synthetically. It is the underlying structure of isoprenoid biochemicals, such as cholesterol, carotenoids, and vitamin A (Hurst 2007, Song et al. 2005). In human breath, isoprene was found to be one of the main endogenous compounds, accounting for up to 70% of exhaled hydrocarbons (Gelmont et al. 1981, Fenske and Paulson 1999, Anderson 2001, Melnick and Sills 2001, Melnick et al. 1996). For example, MAK (2012) reported a weighted multiple-study mean of 64 ± 49 ppb in 337 volunteers. Greater than 200 different plant species, especially trees, emit isoprene (Loreto 1997). The tree species with the highest isoprene emissions are generally in the genera *Quercus* (oaks) and *Populus* (poplars), with *Picea* (spruces) being the only conifer isoprene emitters (Logan et al. 2000).

Global plant production of isoprene is similar to the global production of methane gas (Sharkey 1996, Loreto 1997, Sasaki et al. 2007, Sharkey and Yeh 2001, Sharkey et al. 2007). Isoprene emissions have been estimated to represent 44% of the annual global volatile organic chemical (VOC) flux (Sasaki et al. 2007). Isoprene in the atmosphere also plays an important role in atmospheric chemistry, which includes potentially contributing to ozone formation (Singh et al. 2007, Sasaki et al. 2007, Sharkey 1996, Logan et al. 2000, Loreto 1997, Monson et al. 1994, Loivamaki et al. 2007, Sharkey and Yeh 2001, Sharkey et al. 2007, Guenther et al. 2006, Monson and Holland 2001). Isoprene reacts quickly with hydroxyl ($^{\bullet}OH$) radicals to form hydroperoxides (RO_2), which can convert nitric oxide (NO) to nitrogen dioxide (NO_2), allowing for more ozone (O_3) production (Loreto 1997, Sharkey et al. 2007, Monson and Holland 2001, Guenther et al. 2000).

2.2 Ambient Air Concentrations

Ambient air concentrations of isoprene in Texas are significantly less than central tendency concentrations reported in human breath (e.g., mean human breath concentration of 64 ppb reported in MAK 2012). At ambient air monitoring sites in Texas, isoprene annual averages of

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24-hour (h) and 1-h data range from not detected to 1.26 ppb, with an approximate statewide mean and median of 0.13 and 0.03 ppb, respectively. The vast majority of maximum 24-h and 1-h concentrations at sites across Texas are less than 5 ppb, with all 24-h maximums being below 14 ppb and the majority of 1-h maximums being below 14 ppb (6.4% of the 1-h maximums are greater than 14 ppb) (Texas Air Monitoring Information System (TAMIS) data for 2005-2016).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties

Isoprene is a colorless liquid with a mild aromatic odor and a high vapor pressure. Isoprene is not soluble in water, but is miscible in alcohol and ether. When air concentrations are sufficiently elevated, isoprene is mildly toxic via inhalation and an irritant to the skin, eyes, and mucous membranes. Isoprene is a flammable liquid and can react when exposed to heat, flame, or oxidizers. When liquid isoprene comes into contact with oxygen plus ozone it can ignite. It may also react with air to form unstable peroxides that can be dangerous due to explosive potential (The Merck Index 2001, Sax's Dangerous Properties of Industrial Materials 2000, Hurst 2007). Isoprene at high concentrations (e.g., where oxygen is displaced) may act as an asphyxiant and central nervous system (CNS) depressant (The Merck Index 2001). The main chemical and physical properties are summarized in Table 3.

3.1.2 Key and Supporting Studies

No human epidemiological or experimental toxicity studies were identified for isoprene. Therefore, available acute and subacute animal studies were used for the development of the acute toxicity factors for isoprene.

3.1.2.1 Acute Studies

3.1.2.1.1 Supporting Study – Rohr et al. (2002)

Two acute animal inhalation toxicity studies (Rohr et al. 2002 and Wilkins et al. 2001) were identified for isoprene. Rohr et al. (2002) is a continuation of Wilkins et al. 2001 and used three groups of four male BALB/*c* mice for a total of twelve mice per experiment. Mice were exposed to different combinations of oxidation products, ozone, and terpenes. Terpenes are a large class of hydrocarbons which are generally produced by plants. The terpenes utilized in this study included isoprene, *α*-pinene, and *d*-limonene. Each experiment consisted of a 15-minute pre-exposure period during which animals were exposed to laboratory air alone and breathing parameters were recorded as a baseline. Mice were then exposed for 60 minutes to either air,

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terpene alone, ozone alone, or a terpene/ozone mixture, followed by a 30-minute challenge exposure to either air or terpene alone, and finally a 15-minute recovery period of air exposure. Endpoints examined in this study were sensory irritation, pulmonary irritation, and airflow limitation. Only one dose of isoprene was used in this experiment (465 ppm), which was associated with a mean respiratory frequency reduction of approximately 25% or less over the 105-minute time-course of the experiment. For purposes of this evaluation, 465 ppm is considered a 1-h minimal lowest-observed-adverse-effect-level (LOAEL) for decreased respiratory frequency as an indicator of sensory irritation. This may be very conservative considering that a 30-minute no-observed-effect-level (NOEL) of ≈11,000 ppm was estimated for isoprene-induced sensory irritation in mice in Wilkins et al. 2001 (see below).

3.1.2.1.2 Supporting Study – Wilkins et al. (2001)

Wilkins et al. (2001) evaluated the airway irritation of isoprene, isoprene/ozone, and isoprene/ozone/nitrogen dioxide mixtures in mice. Four male BALB/c mice were exposed (head only) for 30 minutes to either isoprene, isoprene and ozone, or isoprene, ozone, and nitrogen dioxide. Isoprene exposure alone was at 15,000 ppm, and the starting concentrations for the different mixtures were approximately 500 ppm isoprene, 4 ppm ozone, and 4 ppm nitrogen dioxide. Each experiment consisted of a 15-minute pre-exposure period during which animals were exposed to laboratory air alone and breathing parameters were recorded as a baseline. The mice were then exposed for 30 minutes to either mixtures, pure substances, or laboratory air (as listed above), followed by a 15-minute recovery period of air exposure. These parameters were uniformly applied to dose-response experiments for pure substances, mixtures, and air blanks. The mean effect for the period between the 11th and 20th minute of exposure were compared to values obtained during the pre-exposure period to determine the effects of exposure. Data for the pre-exposure period were not significantly different for different groups of mice. To facilitate comparison, differences in effects were expressed as percent of baseline or relative decrease from baseline. The effects evaluated were bronchial constriction, pulmonary irritation, and sensory irritation (as indicated by a decrease in respiratory rate). Sensory irritation was the only effect observed. Exposure to 15,000 ppm isoprene produced a less than 10% decrease in respiratory rate in this study, and a NOEL (i.e., RD_0) of approximately 11,000 ppm was estimated for isoprene-induced sensory irritation.

3.1.2.2 Subacute Studies

3.1.2.2.1 Key Study – NTP (1989)

A National Toxicology Program (NTP) inhalation developmental toxicology study in mice and rats was identified (NTP 1989). Four groups, each consisting of 20 virgin females (10 Sprague-Dawley rats and 10 Swiss (CD-1) mice; for comparison) and approximately 60 positively mated females (28-29 sperm-positive Sprague-Dawley rats and 33 plug-positive Swiss (CD-1) mice),

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were exposed to 0, 280, 1,400, or 7,000 ppm isoprene for 6 hours a day (h/d) 7 days a week (d/wk) for 14 and 12 consecutive days, respectively. Pregnant rats and mice were exposed on days 6 – 19 of gestation and days 6 – 17 of gestation, respectively. Isoprene did not produce maternal or developmental toxicity in the rats. The following were observed in the exposed mouse groups:

- significant reductions in maternal body weight, body weight gain during treatment, and in uterine weight for the 7,000 ppm group;
- exposure-correlated reduction in fetal body weights, which was statistically significant at 280 ppm for female fetuses and 1,400 ppm for male fetuses;
- fetuses of exposed dams had an increased incidence of supernumerary ribs, which was correlated to increasing exposure concentration and was statistically significant for the 7,000 ppm exposure group; and
- two fetuses found with cleft palate, one in each of the two highest exposure groups (1,400 and 1,700 ppm).

A no-observed-adverse-effect-level (NOAEL) of 1,400 ppm was identified for maternal toxicity in mice. No other adverse fetal effects were noted; therefore, a LOAEL of 280 ppm was identified for decreased fetal body weight in female offspring.

This subacute study (NTP 1989) was selected as the key study for derivation of the acute ReV for the following reasons: potential developmental effects due to acute exposure are a concern, this study identifies the lowest LOAEL (280 ppm) relevant to the acute assessment, and moreover, the data are amenable to benchmark dose (BMD) modeling and ultimately result in the lowest human equivalent concentration point of departure (POD_{HEC}).

3.1.2.2.2 Supporting Study – NTP (1994)

A NTP study of isoprene administered by inhalation to F344/N rats and $B6C3F_1$ mice for 2 wks was identified (NTP 1994). This study was a combination of a dose-finding subacute study and two chronic studies.

For the subacute study, groups of 10 males and 10 females per species were exposed to 0, 438, 875, 1,750, 3,500, or 7,000 ppm isoprene for 6 h/d, 5 d/wk for 12 d. No changes were observed in the rats. In the mice, no clinical signs considered to be related to isoprene toxicity were observed. However, the following clinical pathology and histopathology changes were observed in the mice in all exposed groups (outside of controls), unless otherwise stated:

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- decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts in all exposed groups; however, there was no apparent dose-response;
- atrophy of the testis and thymus (observed only in males exposed to 7,000 ppm);
- cytoplasmic vacuolization of the liver (in all male exposed groups);
- olfactory epithelial degeneration in the nasal cavity (only in males exposed to ≥ 1,750 ppm);
- epithelial hyperplasia in the forestomach in all exposed groups, an effect not considered relevant to humans; and
- increases in relative liver weight and decreases in relative spleen weight and final body weight beginning at 438 ppm, with decreases in relative thymus and testis weight beginning at 875 ppm.

Thus, a LOAEL of 438 ppm for male mice (i.e., increased relative liver weight, decreased relative spleen weight and final body weight) and a free-standing NOAEL of 7,000 ppm for rats were identified based on the results of this study. While effects from this study were evaluated as potential critical effects, the POD_{HEC} values resulting from BMD modeling and interspecies dosimetric adjustment were higher than that based on decreased fetal body weight in female offspring (e.g., $BMDL_{10}$/ POD_{HEC} of 274 ppm for increased relative liver weight and 302 ppm for decreased relative spleen weight compared to the POD_{HEC} of 126 ppm for decreased female fetal body weight). Therefore, while the results from this study are supporting, they are not considered further for this assessment.

3.1.3 Metabolism and Mode-of-Action (MOA) Information

Isoprene is formed endogenously at the rate of 0.15 µmol/kg per hour in humans and at the rate of 1.9 µmol/kg per hour in both rats and mice. Environmental exposure from both natural (e.g., vegetation) and anthropogenic sources also occurs (IARC 1999). The metabolic reactions of isoprene are similar to those of 1,3-butadiene (NTP 1989). Isoprene is metabolized by cytochrome P450 (P450), a mixed-function oxidase enzyme. In the P450 enzyme family, CYP2E1 is primarily responsible for isoprene metabolism while CYP2B6 metabolizes isoprene to a lesser extent (Bogaards et al. 2001, Hurst 2007). The P450 metabolites of isoprene are: monoepoxides 3,4-epoxy-3-methyl-1-butene (EPOX I) and 3,4-epoxy-2-methyl-1-butene (EPOX II) and the diepoxide 2-methyl-1,2:3,4-diepoxybutane (Bogaards et al. 2001). The isoprene epoxides (EPOX I and II) can undergo further metabolism via hydrolysis (catalyzed by epoxide hydrolase) and conjugation with glutathione (catalyzed by glutathione S-transferase) into various metabolites (i.e., glutathione conjugates, DIOL I and II, vinyl lactic acid) (Figure 1).

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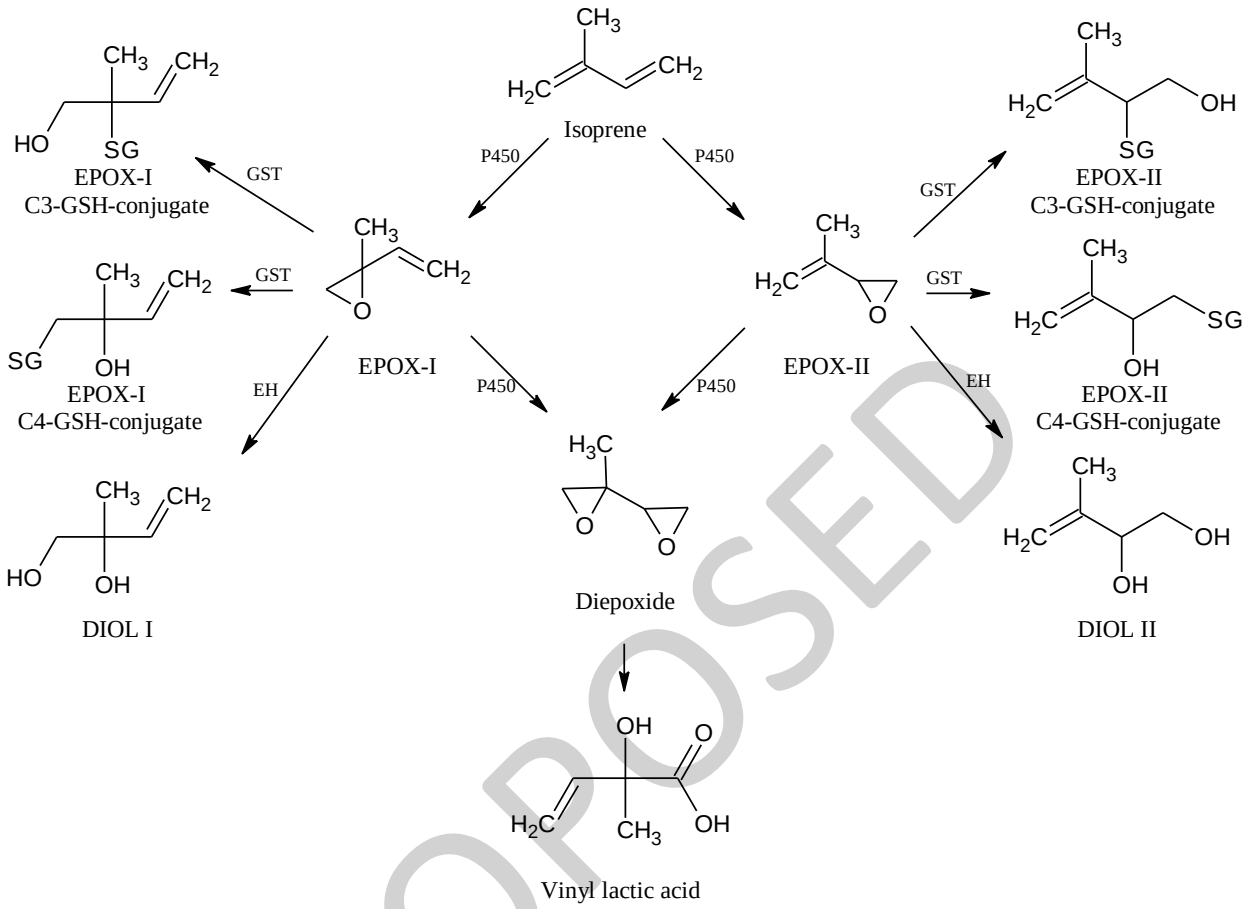

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Figure 1. Metabolic Pathways of Isoprene.
EPOX-I = 3,4-epoxy-3-methyl-1-butene; EPOX-II = 3,4-epoxy-2,methyl-1-butene; GSH = glutathione; P450 = cytochrome P450; GST = glutathione-S-transferase; EH = epoxide hydrolase. Figure adapted from Gervasi and Longo 1990, Melnick et al. 1999, and Bogaards et al. 2001.

The rate of isoprene metabolism is directly proportional to inhalation exposure chamber concentrations of up to approximately 300 ppm, at which point saturation kinetics apply (Peter et al. 1987 as reported in NTP 1989). Additionally, there are significant species differences in metabolism that are important to consider. For example, while the rates of formation of monoepoxides in human, rat, and mouse liver microsomes are roughly similar when epoxide hydrolase is inhibited, under normal conditions the amount of monoepoxides at the end of incubation is 2 and 15 times higher in mouse liver microsomes than in rat and human liver microsomes, respectively (Bogaards et al. 1996 as cited in IARC 1999). Thus, species differences in epoxide hydrolase activity may contribute to species differences in toxicological outcomes (IARC 1999). Additionally, based on toxicokinetic modeling at exposures up to 50 ppm (140

mg/m^3), the rates of metabolism are about 14 times faster in mice and about 8 times faster in rats than in humans (Filser et al. 1996 as cited by IAC 1999). These increased rates are approximately twice those that would be expected based on default allometric body weight scaling (i.e., approximately 7 times faster for mice and 4 times faster for rats). Furthermore, the maximal rate of metabolism *in vivo* is more than three times greater in mice than in rats (IARC 1999, NTP 1994). These toxicokinetic species differences are particularly important to account for when extrapolating animal carcinogenicity study results to humans (e.g., appreciably higher or lower lifetime carcinogenic metabolite concentrations in laboratory animal target tissue compared to humans are indicative of species differences in carcinogenic risk), which was done in the isoprene carcinogenic assessment of Haney et al. (2015)**.**

In regard to the MOA, the isoprene diepoxide metabolite is thought to be responsible for the toxic effects observed in rodents. The amount of isoprene diepoxide ultimately formed is the result of the balance between oxidation by cytochrome P450 and detoxification by epoxide hydrolase and glutathione S-transferase. Therefore, species differences between these enzyme systems may be responsible for the susceptibility to toxic and carcinogenic effects resulting from isoprene exposure (Bogaards et al. 2001).

3.1.4 Dose Metric

Data on the exposure dose of the parent chemical are available in the key study (NTP 1989) and supporting studies. Since data on other more specific dose metrics that may be more closely related to toxicity are not available for the key study (e.g., internal dose metrics such as 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.

3.1.5 Critical Effect and POD for the Key Study

The critical effect is decreased fetal body weight in female offspring. In the key study (NTP 1989), the most sensitive species (i.e., mice) were exposed for 6 h/d, 7 d/wk for 12 d. The 12-d exposure duration is considered subacute according to the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2015a). At the lowest exposure, 280 ppm, fetal female mice showed significantly lower fetal body weights. Therefore, 280 ppm is identified as the LOAEL for this study. Fetal body weight data, which are continuous data, were modeled with BMD Modeling Software (BMDS Version 2.6) using continuous models to derive the POD.

3.1.5.1 Critical Effect Size (CES)

If there is an accepted level of change in the endpoint that is considered to be biologically significant, then that amount of change is chosen for evaluation (USEPA 2000). For dichotomous data, this level is typically expressed as a certain increase in the incidence of

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adverse outcomes and is referred to as the benchmark response (BMR). In order to distinguish continuous data from dichotomous data, Dekkers et al. (2001) recommended the term "critical effect size" (CES) be used instead of the term "BMR," since for continuous data, the effect measure is expressed on a continuous scale. A CES defines the demarcation between non-adverse and adverse changes in toxicological effect parameters for continuous data (Dekkers et al. 2001). Consistent with TCEQ (2015a), since decreased fetal body weight in female mouse offspring is the critical effect, the CES was defined as a 5% relative decrease in the mean when compared to controls (CES_{05}). The CES results for one standard deviation (SD) (CES_{1SD}) from control mean were calculated and are presented in Table 4 for comparison purposes, as suggested by USEPA (2000).

3.1.5.2 Benchmark Concentration Modeling

Female fetal body weight data were modeled using continuous models in USEPA's BMDS Software (Version 2.6). Table 4 contains the dose-response data (i.e., dose, mean, SD, number of litters, percent control response, and coefficient of variation) for the female fetal body weight endpoint.

Table 4. Female Fetal Body Weight Dose-Response Data (NTP 1989)

Dose (ppm)	Female Fetuses (n)	Female Fetal Body Weight [a] (g ± SD)
0	170	1.32 ± 0.10
280	181	1.25 ± 0.10 [b]
1,400	162	1.20 ± 0.10 [b]
7,000	137	1.12 ± 0.13 [b]

[a] Statistically correlated with exposure concentration ($p<0.05$).
[b] Statistically different than controls ($p<0.05$).

Modeling results using the Exponential, Hill, Linear, Polynomial, and restricted Power models did not meet the goodness of fit criterion (p-value > 0.1). Only the unrestricted Power model adequately fit the data (i.e., goodness of fit p-value > 0.1, scaled residual values < |2|, visual inspection). While both a nonhomogeneous and a homogeneous variance were used to model the data, the Akaike's Information Criterion (AIC) was smaller for the nonhomogeneous variance and the test 2 p-value indicated that the variance should be nonhomogeneous. Therefore, the results from the unrestricted Power model with nonhomogeneous variance are reported in Table 5, and Figure 2 illustrates model fit. Decreased fetal body weight had a BMC_{05} of 257.793 ppm and a $BMCL_{05}$ of 126.257 ppm. For comparison, the BMC_{1SD} was 752.17 ppm and the $BMCL_{1SD}$ was 420.857 ppm. The POD for decreased fetal body weight is the $BMCL_{05}$ of 126.257 ppm.

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Table 5. BMC Modeling Results for Reduced Female Mouse Fetal Body Weight – Power (unrestricted) Model [a]

CES	BMC_{05} (ppm)	$BMCL_{05}$ (ppm)	P-value for fit	AIC	Scaled Residual [b]
0.05	257.793	126.257	0.9451	-2260.576267	< |2|
1 SD	752.17	420.857	0.9451	-2260.576267	< |2|

[a] Both nonhomogeneous and homogeneous variances were used to model the data. The AIC for a nonhomogeneous variance was smaller, so the results from a nonhomogeneous variance are reported.
[b] All scaled residuals at each concentration were less than an absolute value of 2 (< |2|)

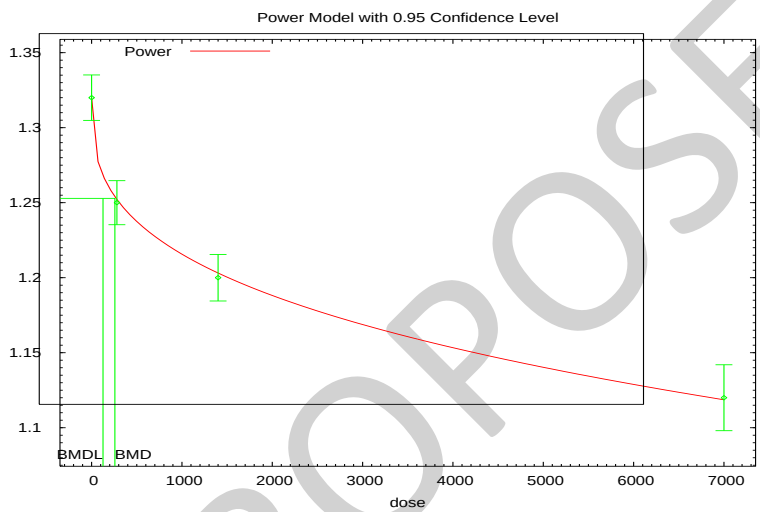

Figure 2. $BMCL_{05}$ Dose-Response for Decreased Female Mouse Fetal Body Weight
$BMCL_{05}$ = 126.257 ppm (unrestricted power model).

3.1.6 Dosimetric Adjustments

3.1.6.1 Default Exposure Duration Adjustments

Reduced fetal body weight is considered a developmental endpoint. Since the POD is derived from a developmental endpoint, the 6-h exposure duration will conservatively not be adjusted to 1 h per TCEQ Guidelines (TCEQ 2015a). The $BMCL_{05}$ of 126.257 ppm is the POD for the critical effect of decreased female fetal body weight.

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3.1.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Isoprene produces both respiratory and remote effects. Isoprene is therefore classified as a Category 2 gas. According to the TCEQ Guidelines (2015a), dosimetry for Category 2 gases is under review by USEPA. Until new findings suggest otherwise, dosimetric adjustments for Category 2 gases will be conducted using either Category 1 or 3 dosimetry equations, whichever is most relevant. The most relevant dosimetry classification for isoprene based on the critical effect is Category 3, because the critical effect is decreased fetal weight in female offspring, which is a remote effect. For Category 3 gases:

$$POD_{HEC} = POD_{ADJ} x \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

where:
$H_{b/g}$ = blood:gas partition coefficient
A = animal
H = human

For isoprene, the blood:gas partition coefficients for mice and humans are 2.04 and 0.75, respectively (Filser et al. 1996). If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the regional gas dose ratio (RGDR) (USEPA 1994).

$$POD_{HEC} = POD_{ADJ} x \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 126.257\, ppm\ x\ 1$$

$$= 126.257\, ppm$$

3.1.7 Application of Uncertainty Factors to the POD_{HEC}

The critical effect is decreased fetal body weight in female offspring. The default for threshold effects is to determine a POD_{HEC} and apply uncertainty factors (UFs) to derive the ReV (i.e., assume a threshold MOA) (TCEQ 2015a). Therefore, appropriate UFs were applied to the POD_{HEC} to derive the acute ReV. More specifically, the acute 6-h ReV was calculated from the subacute POD_{HEC} using an interspecies uncertainty factor (UF_A) of 3, an intraspecies UF (UF_H) of 10, and a database UF (UF_D) of 3, for a total UF = 90.

- An UF_A of 3 was used because the default dosimetric adjustment accounts for toxicokinetic differences, but does not account for toxicodynamic species differences.

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- An UF_H of 10 was used to account for variability within the human population (e.g., adult/child differences, those with pre-existing medical conditions).
- An UF_D of 3 was used because the database confidence is medium-to-high, according to evaluation under Table 4-2 in the TCEQ Guidelines (TCEQ 2015a); there are relevant acute/subacute studies in two species (e.g., consideration of multiple-day subacute study results is generally conservative for developing acute values of shorter duration; for example, effects such as reduced body weight/fetal weight may very well be the result of multiple days of exposure), and there is also a reproductive/developmental study available.

$$acute\ ReV = \frac{POD_{HEC}}{UF_A\ x\ UF_H\ x\ UF_D}$$

$$= \frac{126.257\ ppm}{(3\ x\ 10\ x\ 3)} = \frac{126.257\ ppm}{90}$$

$$= 1.403\ ppm\ or\ 1{,}400\ ppb\ (3{,}900\ \mu g/m^3)\ round\ to\ two\ significant\ digits$$

3.1.8 Acute 6-h ReV and ^{acute}ESL

In deriving the acute 6-h ReV, no numbers were rounded between equations. Once the ReV was calculated, it was rounded to 2 significant digits. The rounded acute ReV was then multiplied by 0.3 to calculate the ^{acute}ESL, and the ^{acute}ESL subsequently rounded. The resulting acute 6-h ReV is 1,400 ppb (3,900 µg/m^3), and the ^{acute}ESL is 420 ppb (1,200 µg/m^3) (Table 5).

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Table 4. Derivation of the Acute 6-h ReV and ^{acute}ESL

Parameter	Summary
Study	NTP 1989
Study population	Approximately 30 positively mated female Swiss (CD-1) mice per exposure group
Study quality	High
Exposure Methods	Whole-body exposure to isoprene vapor at 0, 280, 1400, 7000 ppm
Critical Effects	Decreased female fetal body weight
POD (original study)	126.257 ppm ($BMCL_{05}$)
Exposure Duration	6 h/d, 7 d/wk for 12 d
Extrapolation to 1 h	No adjustment because the critical effect was a developmental endpoint
POD (6 h)	126.257 ppm
6-h POD_{HEC}	126.257 ppm (gas with systemic effects, based on default RGDR = 1)
Total uncertainty factors (UFs)	90
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Database UF	3
Database Quality	Medium-to-high
Acute 6-h ReV (HQ = 1)	**1,400 ppb (3,900 µg/m^3)**
^{acute}ESL (HQ = 0.3)	**420 ppb (1,200 µg/m^3)**

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3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Isoprene is described as having a mild aromatic odor. The acute odor-based ESL ($^{acute}ESL_{odor}$) for isoprene, using an evidence-integration approach as described in the Approaches to Derived Odor-Based Values (TCEQ 2015b), is 130 µg/m^3 (48 ppb).

3.2.2 Vegetation Effects

No studies could be identified in which isoprene air concentrations had adverse effects on vegetation. In fact, isoprene emissions are naturally produced by plants. Information on vegetation as a source of isoprene is discussed in Chapter 2.

3.3 Short-Term Values

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

- acute ReV = 3,900 µg/m^3 (1,400 ppb)
- ^{acute}ESL = 1,200 µg/m^3 (420 ppb)
- ^{acute}ESL$_{odor}$ = 130 µg/m^3 (48 ppb)

The short-term ESL for air permit reviews is the odor-based ^{acute}ESL$_{odor}$ of 130 µg/m^3 (48 ppb) (Table 1). For the evaluation of air monitoring data, the ^{acute}ESL$_{odor}$ of 130 µg/m^3 (48 ppb), as well as the acute ReV of 3,900 µg/m^3 (1,400 ppb), may be used (Table 1). The ^{acute}ESL is not used to evaluate ambient air monitoring data.

3.4 Subacute Inhalation Observed Adverse Effect Level (IOAEL)

Risk assessors, and the general public, often ask to have information on the levels in air where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific IOAELs in DSDs (TCEQ 2015a). As the basis for development of IOAELs is limited to available data, future studies could possibly identify a lower POD for this purpose. Regarding critical effects due to subacute isoprene exposure, the animal study of NTP (1989) provides a BMC$_{05}$ of 258 ppm (720 mg/m^3) for reduced female fetal weight due to 6 h/day, multiple day (i.e., subacute) exposure. This animal POD was used as the animal subacute IOAEL for extrapolation to humans. No duration adjustment was made (TCEQ 2015a). In producing reduced fetal weight (a systemic effect), isoprene acted as a Category 3 gas. The default pharmacokinetic animal-to-human dosimetric adjustment for a Category 3 gas is multiplication of the animal-based POD by the ratio of the animal/human blood:gas partition coefficients (TCEQ 2015a). Consistent with Section 3.1.6.2, a default value of 1 was used for the RGDR. Thus, following animal-to-human dosimetric adjustment, the subacute POD$_{HEC}$ is 258 ppm (720 mg/m^3). This POD$_{HEC}$ determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the subacute study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The subacute IOAEL of 258 ppm (720 mg/m^3) is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the estimated subacute IOAEL of 258 ppm (720 mg/m^3) and the 6-h acute ReV of 1.4 ppm (3.9 mg/m^3) is a factor of 184.

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Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Key and Supporting Studies

Two studies were identified that investigated occupational exposure to isoprene (Lynch 2001, Leber 2001). However, these studies only provide monitoring data on isoprene to assess exposure; they do not provide information on any health effects experienced due to exposure. Therefore, these studies are not useful for the chronic evaluation. Due to the lack of human data, animal studies were considered for the development of a chronic ReV for isoprene.

The key chronic study is from NTP (1994), a toxicity study of isoprene administered by inhalation to F344/N rats and B6C3F$_1$ mice. The NTP (1994) study was a combination of a dose-finding, subacute study, a 13-wk (i.e., 90-d) subchronic study, and a 6-month chronic study. The chronic portion will serve as the key study, while results from the subchronic portion will be used as supporting data.

4.1.1.1 Key Study - Chronic Portion of NTP (1994)

For the chronic stop-exposure study, groups of 40 male rats and 40 male mice were exposed to 0, 70, 220, 700, 2,200, or 7,000 ppm isoprene for 6 h/d, 5 d/wk for 6 months. Ten animals per species were evaluated at the end of the exposure, while the rest were allowed to recover for an additional 6 months without isoprene exposure (i.e., the stop-exposure portion of the study). Testicular interstitial cell hyperplasia was observed in all male rats exposed to 7,000 ppm. No other adverse effects were noted in rats. In the mice, the following effects were observed:

- partial hindlimb paralysis, primarily in the 7,000 ppm groups, and significantly decreased forelimb and hindlimb grip strength in the 220 ppm and greater groups (e.g., hindlimb grip strength was monotonically decreased across all exposure groups), both of which were not statistically different than controls at the end of the 6-month recovery period;
- nonresponsive macrocytic anemia similar to that observed in the 13-wk study, evidenced by lower erythrocyte counts, hemoglobin concentrations, and hematocrit values, and greater mean cell volume values in the 700, 2,200, and 7,000 ppm groups;
- significantly greater relative liver weights in the 7,000 ppm group, and after 6 months of recovery, significantly greater relative liver weights in the 700, 2,200, and 7,000 ppm groups;

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- skeletal muscle atrophy, sciatic nerve degeneration, and spinal cord degeneration in the 7,000 ppm groups (all but the spinal cord degeneration resolved after 6 months of recovery);
- significant decrease in relative testis weights, along with testicular atrophy, in the 7,000 ppm group, both of which resolved after 6 months of recovery;
- significant decrease in relative spleen weights in the 700, 2,200, and 7,000 ppm groups, which resolved for the 700 ppm and 2,200 ppm groups after 6 months of recovery;
- after 6 months of recovery, relative brain weights in the 700, 2,200, and 7,000 ppm groups were significantly less than controls;
- olfactory epithelial degeneration and chronic inflammation of the olfactory epithelium in the 7,000 ppm male group, which did not regress during the 6-month recovery period; and
- epithelial hyperplasia of the forestomach in 700 ppm or greater exposure groups (increases were still observed after the 6-month recovery period); however, epithelial hyperplasia of the forestomach is not an effect considered to be relevant to humans.

The TCEQ identified a NOAEL of 70 ppm and a LOAEL of 220 ppm for decreased forelimb and hindlimb grip strength in mice and a NOAEL of 2,200 ppm and a LOAEL of 7,000 ppm for testicular interstitial cell hyperplasia in rats based on the results from this study. Decreased forelimb and hindlimb grip strength in mice was the most sensitive effect identified based on the reported results. While other effects from this study were evaluated as potential critical effects, the POD_{HEC} values resulting from BMD modeling and interspecies dosimetric adjustment were higher than that based on decreased forelimb and hindlimb grip strength (e.g., $BMDL_{10}/POD_{HEC}$ of 122 ppm for increased relative liver weight and 194 ppm for decreased relative spleen weight compared to the POD_{HEC} of 70 ppm for decreased forelimb and hindlimb grip strength).

4.1.1.2 Supporting Study - Subchronic Portion of NTP (1994)

For the subchronic (i.e., 90-d) study, groups of 10 males and 10 females per species were exposed to 0, 70, 220, 700, 2,200, or 7,000 ppm isoprene for 6 h/d, 5 d/wk for 13 weeks. No discernible toxicological effects were observed in rats. In the mice, the following toxic effects were induced at multiple organ sites:

- nonresponsive macrocytic anemia, as evidenced by greater mean cell volume values than controls in the 220 ppm or greater groups;
- decreased leukocyte, neutrophil, lymphocyte, and bone marrow cellularity counts in the 7,000 ppm male mice group;

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- liver and lung tissue glutathione concentrations were approximately 40% to 60% lower than controls in the 7,000 ppm groups;
- decreases in relative testis weights as compared to controls in male mice exposed to 2,200 or 7,000 ppm;
- decreases in relative spleen weights in the 700, 2,200, and 7,000 ppm male mice groups;
- increases in relative liver weights in the 220, 700, 2,200, and 7,000 ppm female mice groups and in the 7,000 ppm male mice group;
- increases in relative kidney weights in the 220, 700, 2,200, and 7,000 ppm female mice groups;
- olfactory epithelial degeneration and chronic inflammation of the olfactory epithelium in male mice exposed to 7,000 ppm; and
- epithelial hyperplasia of the forestomach in 700 ppm or greater groups, an effect not relevant for humans.

The TCEQ identified a NOAEL of 70 ppm and a LOAEL of 220 ppm for nonresponsive macrocytic anemia in mice and a free-standing NOAEL of 7,000 ppm for rats based on the results from this study. The subchronic NOAEL and LOAEL values for macrocytic anemia in mice are the same as, and support, those for decreased forelimb and hindlimb grip strength in mice due to chronic exposure.

4.1.2 Consideration of Developmental/Reproductive Effects

While a multigenerational reproductive study is not available, an NTP developmental study is available for isoprene (NTP 1989). In fact, the acute 6-h ReV is based on results of the developmental study (NTP 1989); more specifically, the developmental effect of decreased fetal body weight. As indicated in Section 3.1.5.2, decreased female fetal body weight had a BMC_{05} of 257.793 ppm in mice. This POD is similar to, but slightly higher than, the LOAEL of 220 ppm for decreased forelimb and hindlimb grip strength in mice, which results in a lower POD_{HEC}. Thus, decreased forelimb and hindlimb grip strength in mice is the critical effect for derivation of the chronic ReV. Ultimately, dosimetric adjustments and the application of appropriate UFs to derive the chronic ReV results in a value 10-fold lower than the acute 6-h ReV (see below). Therefore, the chronic ReV is expected to be protective of potential developmental/reproductive effects.

4.1.3 MOA Analysis and Dose Metric

The MOA is discussed in Section 3.1.2. Data on the exposure concentration of the parent chemical is available in the key study (NTP 1994). Since data on other more specific dose

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metrics that may be more closely related to toxicity are not available for the key study (e.g., internal dose metrics such as 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.

4.1.4 Critical Effect and POD for the Key Study

The critical effect is decreased forelimb and hindlimb grip strength in mice. A NOAEL of 70 ppm was identified for this effect from NTP (1994).

4.1.5 Dosimetric Adjustments

4.1.5.1 Exposure Duration Adjustments

Since the exposure was not continuous, the POD was adjusted to a continuous exposure duration:

$$POD_{ADJ} = POD\ x\ \frac{D}{24\ h}\ x\ \frac{F}{7\ d}$$

where:
POD_{ADJ} = POD from animal studies, adjusted to a continuous exposure
POD = POD from animal studies, based on a discontinuous exposure
D = exposure duration, hours per day
F = exposure frequency, days per week

$$POD_{ADJ} = 70\ ppm\ x\ \frac{6\ h}{24\ h}\ x\ \frac{5\ d}{7\ d}$$

$$= 12.5\ ppm$$

$$= 12{,}500\ ppb$$

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Isoprene produces both respiratory and remote effects. Isoprene is therefore classified as a Category 2 gas. According to the TCEQ Guidelines (2015a), dosimetry for Category 2 gases is under review by USEPA. Until new findings suggest otherwise, dosimetric adjustments for Category 2 gases will be conducted using either Category 1 or 3 dosimetry equations, whichever is most relevant. The most relevant dosimetry classification for isoprene is Category 3 based on the critical effect of decreased forelimb and hindlimb grip strength in mice, which are remote effects. For Category 3 gases:

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$$POD_{HEC} = POD_{ADJ} x \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

where:
Hb/g = blood:gas partition coefficient
A = animal
H = human

For isoprene, the blood:gas partition coefficients for mice and humans are 2.04 and 0.75, respectively (Filser et al. 1996). If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the RGDR (USEPA 1994)

$$POD_{HEC} = POD_{ADJ} x \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 12{,}500\ ppb\ x\ 1$$

$$= 12{,}500\ ppb$$

4.1.6 Application of UFs to the POD_{HEC}

The critical effect is decreased forelimb and hindlimb grip strength in mice. The default for threshold effects is to determine a POD_{HEC} and apply UFs to derive the ReV (i.e., assume a threshold MOA) (TCEQ 2015a). Therefore, appropriate UFs were applied to the POD_{HEC} to derive the chronic ReV. More specifically, the chronic ReV was calculated from the chronic POD_{HEC} using an UF_A of 3, an UF_H of 10, and an UF_D of 3, for a total UF = 90.

- An UF_A of 3 was used because the default dosimetric adjustment accounts for toxicokinetic differences, but does not account for toxicodynamic species differences.
- An UF_H of 10 was used to account for any variability within the human population (e.g., adult/child differences, those with pre-existing medical conditions).
- An UF_D of 3 was used because the database confidence is medium, consistent with evaluation under Table 5-2 in the TCEQ Guidelines (TCEQ 2015a). For example, while subchronic and chronic studies and a developmental study (NTP 1989) were available in both mice and rats, a multigenerational reproductive study was not available.

$$chronic\ ReV = \frac{POD_{HEC}}{UF_A\ x\ UF_H\ x\ UF_D}$$

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$$= \frac{12{,}500\ ppb}{(3\ x\ 10\ x\ 3)} = \frac{12{,}500\ ppb}{90}$$

$$= 140\ ppb\ (390\ \mu g/m^3)\ round\ to\ two\ significant\ digits$$

4.1.7 Chronic ReV and ^{chronic}ESL

In calculating the chronic ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to 2 significant figures. The rounded ReV was then multiplied by 0.3 to calculate the ESL, and the ESL subsequently rounded. The resulting chronic ReV is 140 ppb (390 µg/m^3), and the $^{chronic}ESL_{threshold(nc)}$ is 42 ppb (120 µg/m^3) (Table 7).

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Table 5. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Summary
Study	NTP 1994
Study Population	40 male F344/N rats; 40 male B6C3F1 mice
Study Quality	High (GLP)
Exposure Method	Inhalation exposure at 0, 70, 220, 700, 2,200, and 7,000 ppm
Critical Effects	In mice: decreased forelimb and hindlimb grip strength
POD (original study)	70,000 ppb (NOAEL)
Exposure Duration	6 h/d, 5 d/wk for 13-wk or 6-mo
POD_{ADJ} (extrapolation to continuous exposure)	12,500 ppb
POD_{HEC}	12,500 ppb
Total UFs	90
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	NA
Subchronic to chronic UF	NA
Database UF	3
Database Quality	Medium
Chronic ReV (HQ = 1)	**140 ppb (390 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**42 ppb (120 µg/m^3)**

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4.2 Carcinogenic Potential

Isoprene is the 2-methyl analog of 1,3-butadiene, an industrial chemical that has been identified as an animal and human carcinogen. According to the National Toxicity Program's 13th Report on Carcinogens (NTP 2014), isoprene is “reasonably anticipated to be a human carcinogen” based on sufficient evidence of carcinogenicity from studies in experimental animals (i.e., tumors at several different tissue sites in mice and rats). For example, inhalation exposure to isoprene induced increased incidences of neoplasms of the liver, lung, and hematopoietic system in mice (Placke et al. 1996). However, a carcinogenic dose-response assessment for inhalation exposure to isoprene has not been conducted by human health assessment programs such as the Integrated Risk Information System of the USEPA or the

Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency. The TCEQ performs carcinogenic dose-response assessments for chemicals considered "likely to be carcinogenic to humans", particularly when a suitable dose-response assessment conducted by another agency is not available for adoption (TCEQ 2015a). Accordingly, an initial draft carcinogenic dose-response assessment was conducted and peer reviewed in 2013. Substantial interspecies differences in metabolism, use of the best estimate exposure concentration at a 10% response level (EC_{10}) for malignancies for the POD, and the undue conservativeness (i.e., over-protectiveness) of a derivation process leading to a 1 in 100,000 no significant excess risk air concentration significantly less than that normally found in human breath (due to endogenous production) were identified as important considerations, with implications for the dose-response assessment, to be addressed in a final carcinogenic assessment. The TCEQ has recently published an updated carcinogenic assessment and URF derivation for isoprene that addresses these considerations in a scientific peer-reviewed journal manuscript (Haney et al. 2015).

Haney et al. (2015) present the procedures used in the carcinogenic assessment of isoprene and the derivation of the URF based on the evaluation of three laboratory animal studies with adequate data to perform dose-response modeling (NTP 1994, 1999; Placke et al. 1996). Ultimately, the URF of 6.2E-08 per ppb (2.2E-08 per mg/m^3) was based on the 95% lower confidence limit on the effective concentration corresponding to 10% extra risk (LEC_{10}) for liver carcinoma in male B6C3F1 mice, after incorporating appropriate adjustment factors for species differences in target tissue metabolite concentrations (i.e., interspecies differences in metabolism) and inhalation dosimetry. The corresponding lifetime air concentration at the 1 in 100,000 no significant excess risk level is 160 ppb (450 mg/m^3). This concentration is almost 4,400 times lower than the lowest exposure level associated with statistically increased liver carcinoma in B6C3F1 mice in the key study (700 ppm in Placke et al. 1996) and is above typical isoprene breath concentrations (due to endogenous production) reported in the scientific literature (e.g., median of 52 ppb in 344 health fair attendees in Moser et al. 2005; weighted multiple-study mean of 64 ± 49 ppb in 337 volunteers in MAK 2012). Continuous lifetime environmental exposure to the 1 in 100,000 excess risk level of 160 ppb would be expected to raise the human blood isoprene area under the curve (AUC) less than one-third of the standard deviation (SD) of the endogenous mean blood AUC. An isoprene air concentration corresponding to ≤ 1 SD of the endogenous mean blood AUC would be expected to make an insignificant contribution to lifetime cancer risk (MAK 2012). By comparison, ambient air monitoring sites in Texas measure annual concentrations that are orders of magnitude lower, ranging from not detected to 1.26 ppb, with an approximate statewide mean of 0.13 ppb (TAMIS data for 2005-2016).

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In conclusion, the URF for isoprene (6.2E-08 per ppb or 2.2E-08 per mg/m^3) developed in Haney et al. (2015) and the corresponding 1 in 100,000 excess risk level (160 ppb or 450 mg/m^3) are considered sufficiently health-protective for use in protecting the general public against the potential carcinogenic effects of chronic exposure to isoprene in ambient air. That peer-reviewed publication, which is open access, serves as documentation of the assessment of the carcinogenic potential of isoprene for the purposes of this DSD.

4.3 Welfare-Based Chronic ESLs

Since isoprene is produced largely by plants, the TCEQ found several studies that discussed the natural production of isoprene by plants. Information on vegetation as a source of isoprene is discussed in Chapter 2. However, no studies could be identified in which isoprene had adverse effects on vegetation.

4.4 Long-Term Values

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

- chronic ReV = 390 µg/m^3 (140 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 120 µg/m^3 (42 ppb)
- $^{chronic}ESL_{nonthreshold(c)}$ = 450 µg/m^3 (160 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 120 µg/m^3 (42 ppb). For the evaluation of air monitoring data, the chronic ReV of 390 µg/m^3 (140 ppb), as well as the $^{chronic}ESL_{nonthrehold(c)}$ of 450 µg/m^3 (160 ppb), may be used. The $^{chronic}ESL_{threshold(nc)}$ is not used to evaluate ambient air monitoring data.

4.5 Chronic IOAEL

Risk assessors, and the general public, often ask to have information on the levels in air where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific IOAELs in DSDs (TCEQ 2015a). As the basis for development of IOAELs is limited to available data, future studies could possibly identify a lower POD for this purpose. Regarding critical effects due to chronic isoprene exposure, the animal study of NTP (1994) provides a LOAEL of 220 ppm for decreased forelimb and hindlimb grip strength in mice due to chronic exposure. This animal POD was used as the animal chronic IOAEL for extrapolation to humans. No duration adjustment was made (TCEQ 2015a). In producing reduced grip strength (a systemic effect), isoprene acted as a Category 3 gas. The default pharmacokinetic animal-to-human dosimetric adjustment for a Category 3 gas is multiplication of the animal-based POD by the ratio of the animal/human blood:gas partition coefficients (TCEQ 2015a). Consistent with Section 4.1.6.2, a default value of 1 was used for the RGDR. Thus, following animal-to-human dosimetric adjustment, the chronic POD_{HEC} is 220 ppm (610 mg/m^3). This POD_{HEC} determined

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from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level chronically. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic IOAEL of 220 ppm (610 mg/m^3) is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the estimated chronic IOAEL of 220 ppm (610 mg/m^3) and the chronic ReV of 0.14 ppm (0.39 mg/m^3) is approximately a factor of 1,570.

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