Development Support Document
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Trimethylbenzenes

CAS Registry Numbers:

526-73-6 (1,2,3-TMB)
95-63-6 (1,2,4-TMB)
108-67-8 (1,3,5-TMB)
25551-13-7 (Mixed Isomers)

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TABLE OF CONTENTS

TABLE OF CONTENTS ..... **I**

LIST OF TABLES ..... **II**

ACRONYMS AND ABBREVIATIONS ..... **III**

CHAPTER 1 SUMMARY TABLES **1**

CHAPTER 2 MAJOR SOURCES AND USES **4**

CHAPTER 3 ACUTE EVALUATION **4**

3.1 HEALTH-BASED ACUTE REV AND ^{ACUTE}ESL 4
3.1.1 Physical/Chemical Properties *4*
3.1.2 Key and Supporting Studies *4*
3.1.2.1 Human Studies 5
3.1.2.1.1 Key Human Study (Järnberg et al. 1996) 6
3.1.2.1.2 Supporting Human Study (Kostrzewski et al. 1997) 6
3.1.2.2 Animal Studies 7
3.1.2.2.1 Key Animal Study (Korsak and Rydzynski 1996) 7
3.1.2.2.2 Supporting Animal Studies 10
3.1.2.3 Developmental and Reproductive Studies 11
3.1.3 Mode-of-Action (MOA) Analysis *14*
3.1.4 Point of Departure (POD) for Key Study and Critical Effect *15*
3.1.5 Dosimetric Adjustments *15*
3.1.6 Adjustments of the POD_{HEC} and Application of Uncertainty Factors *16*
3.1.7 Health-Based Acute ReV and ^{acute}ESL *16*
3.2 WELFARE-BASED ACUTE ESLS 17
3.2.1 Odor Perception *17*
3.2.2 Vegetation Effects *17*
3.3 SHORT-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 17
3.4 ACUTE INHALATION OBSERVED ADVERSE EFFECT LEVEL 18

CHAPTER 4 CHRONIC EVALUATION **19**

4.1 NONCARCINOGENIC POTENTIAL 19
4.1.1 Physical/Chemical Properties *19*
4.1.2 Key and Supporting Studies *19*
4.1.2.1 Human Studies 19
4.1.2.2 Animal Studies 19
4.1.2.2.1 Key Animal Study 20
4.1.2.2.2 Supporting Animal Studies 21
4.1.2.3 Developmental and Reproductive Studies 22
4.1.3 MOA Analysis *25*
4.1.4 Key Study PODs, Dosimetric Adjustments, and Critical Effect *25*
4.1.4.1 Dosimetric Adjustments and POD for 1,2,4-TMB 25
4.1.4.2 POD and Dosimetric Adjustments for 1,2,3-TMB 26
4.1.4.3 Key Study POD and Critical Effect 26
4.1.5 Adjustments of the POD_{HEC} and Application of UFs *26*
4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ *29*
4.2 CARCINOGENIC POTENTIAL 31
4.3 WELFARE-BASED CHRONIC ESL 31

4.4 LONG-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION 31
4.5 SUBCHRONIC INHALATION OBSERVED ADVERSE EFFECT LEVEL 32

CHAPTER 5 REFERENCES.....33

LIST OF TABLES

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air 1
Table 2. Air Permitting Effects Screening Levels (ESLs) 2
Table 3. Chemical and Physical Data 3
Table 4. Derivation of the Acute ReV and ^{acute}ESL 17
Table 5. Derivation of the Chronic ReV and ^{chronic}ESL 30

Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AMCV	Air Monitoring Comparison Value
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMR	benchmark response
°C	degrees Celsius
C9	nine carbon aromatic hydrocarbon compounds
cm	centimeter
CNS	central nervous system
DSD	development support document
EC	effective concentration
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
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effect
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effects
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects

Acronyms and Abbreviations	Definitions
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
h	hour(s)
H	humans
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
MOA	mode of action
n	number
NCEA	National Center for Environmental Assessment
NOAEL	no-observed-adverse-effect-level
NRC	National Research Council
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

Acronyms and Abbreviations	Definitions
ReV	reference value
SCE	sister chromatid exchange
SD	standard deviation
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TMB(s)	trimethylbenzene(s)
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
UV	ultraviolet
WOE	weight of evidence

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values resulting from an acute and chronic evaluation of trimethylbenzenes (TMBs). 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 TMB's physical/chemical properties.

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

Short-Term Values	Concentration	Notes
Acute ReV	15,000 µg/m^3 (3,000 ppb) **Short-Term Health**	**Critical Effect(s):** Based on a free-standing human NOAEL, with neurotoxicity (e.g., impaired rotarod performance) in rats as the critical effect at higher concentrations
$^{acute}ESL_{odor}$	---	Strong, pleasant aromatic odor
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	180 µg/m^3 (37 ppb) **Long-Term Health**	**Critical Effect(s):** Neurotoxicity (e.g., decreased pain sensitivity) in rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; h, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; **$^{chronic}ESL_{threshold(nc)}$**, chronic health-based ESL for threshold dose-response noncancer effects; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

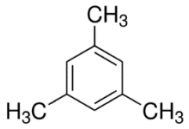
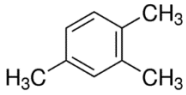
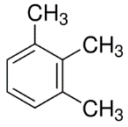
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	4,400 µg/m^3 (900 ppb)[a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Based on a free-standing human NOAEL, with neurotoxicity (e.g., impaired rotarod performance) in rats as the critical effect at higher concentrations
$^{acute}ESL_{odor}$	---	Strong, pleasant aromatic odor
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	54 µg/m^3 (11 ppb)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Neurotoxicity (e.g., decreased pain sensitivity) in rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] Based on the acute ReV of 15,000 µg/m^3 (3,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 180 µg/m^3 (37 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	1,3,5-TMB	1,2,4-TMB	1,2,3-TMB	Reference
Molecular Formula	C_9H_{12}	C_9H_{12}	C_9H_{12}	NRC 2012
Chemical Structure				NRC 2012
Molecular Weight	120.19	120.19	120.19	NRC 2012
Physical State at 25°C	Liquid	Liquid	Liquid	NRC 2012
Color	Clear	Clear	Clear	USEPA 2013
Odor	Pleasant aromatic	Pleasant aromatic	Pleasant aromatic	ACGIH 2001
CAS Registry Number	108-67-8	95-63-6	526-73-8	NRC 2012
Synonyms	Mesitylene	Pseudocumene	Hemimellitene	NRC 2012
Solubility in water (mg/L)	51.5 (practically insoluble)	56.8 (practically insoluble)	75.2 (practically insoluble)	TRRP 2014 NRC 2012
Log K_{ow}	3.7	3.65	3.55	TRRP 2014
Vapor Pressure	1.5 mm Hg at 25°C	2.0 mm Hg at 25°C	2.5 mm Hg at 25°C	NRC 2012
Relative Vapor Density (air = 1)	4.1	4.15	4.1	NRC 2012
Melting Point	-44.8°C	-43.78°C	-25.4°C	NRC 2012 ChemSpider 2015
Boiling Point	164°C	169°C	176°C	NRC 2012
Conversion Factors	1 $\mu g/m^3$ = 0.203 ppb 1 ppb = 4.92 $\mu g/m^3$	1 $\mu g/m^3$ = 0.203 ppb 1 ppb = 4.92 $\mu g/m^3$	1 $\mu g/m^3$ = 0.203 ppb 1 ppb = 4.92 $\mu g/m^3$	NRC 2012

Chapter 2 Major Sources and Uses

The commercially available substance known as TMBs (CAS No. 25551-13-7) is a mixture of three isomers in various proportions: 1,2,3-TMB or hemimellitene (CAS No. 526-73-8), 1,2,4-TMB or pseudocumene (CAS No. 95-63-6), and 1,3,5-TMB or mesitylene (CAS No. 108-67-8). Production of TMB isomers occurs during petroleum refining, and 1,2,4-TMB individually makes up approximately 40% of the C9 aromatic fraction (i.e., aromatic hydrocarbons with nine carbons). Vehicle emissions are a major anthropogenic source of TMBs, due to the widespread use of the C9 fraction as a component of gasoline. Other uses of TMBs include solvents in research and industry, dyestuff intermediate, paint thinner, and as a UV oxidation stabilizer for plastics. Occupational levels of exposure for TMBs have been measured between 20-8,540 $\mu g/m^3$, whereas residential exposures are generally much lower at 0.29-7.8 $\mu g/m^3$ (USEPA 2013). Maximum 24-hour (h) ambient air levels in Texas generally range from nondetect to 29 $\mu g/m^3$ (6 ppb), with annual means from nondetect to 1.4 $\mu g/m^3$ (0.28 ppb) (2010-2014 data from TCEQ's Texas Air Monitoring Information System (TAMIS) database).

Chapter 3 Acute Evaluation

The Development Support Document (DSD) is a summary of the key and supporting studies and procedures used by the Toxicology Division (TD) to derive inhalation toxicity values. This section is based on a review of current literature as well as background readings in NRC (2012), ACGIH (2001), NCEA (2007, 2009, 2010), and USEPA (2013), which describe the toxicity of TMBs in greater detail.

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

3.1.1 Physical/Chemical Properties

TMBs are aromatic hydrocarbons with three methyl groups attached to a benzene ring and the chemical formula C_9H_{12}. Together with other compounds of the same empirical formula, these substances are referred to as the C9 aromatics. The chemical and physical properties of the three TMB isomers are similar to one another and are summarized in Table 3. Based on their vapor pressures, 1,2,3-, 1,2,4-, and 1,3,5-TMB exist solely in the vapor phase under ambient conditions. The degradation of TMBs in the atmosphere occurs by reaction with hydroxyl radicals, the half-life of which is 11-12 h. TMBs are colorless, flammable liquids with a strong aromatic odor.

3.1.2 Key and Supporting Studies

Human data are preferred for derivation of the acute ReV and ESL (TCEQ 2015a). In regard to occupational studies, data on the acute adverse health effects of TMB exposure are limited. Because human occupational studies involve exposure to mixtures containing multiple TMB isomers and other volatile organic compounds, ascertaining the specific contribution of each TMB isomer to the health effects reported is difficult. Information is available from controlled

human exposure pharmacokinetic studies to individual isomers (Järnberg et al. 1996, Kostrzewski et al. 1997); while these acute studies do not report adverse health effects (i.e., are not informative as to the specific critical effect), they are informative in regard to no-observed-adverse-effect-level (NOAEL) values for the acute effects evaluated such as central nervous system (CNS) effects and irritation in humans.

The laboratory animal toxicity database is more robust and informative as to critical effect(s) resulting from exposure to TMBs. Animal inhalation studies of TMBs include short-term studies that report such effects as neurological effects (e.g., decreased pain sensitivity, altered cognitive function, and decreased anxiety and/or increased motor function) and respiratory irritation (e.g., decreased respiration rates). However, neurological (i.e., CNS function) effects, including decreased pain sensitivity (i.e., in the hot plate test) and decreased neuromuscular function and coordination (i.e., in the rotarod test), appear to be the most sensitive endpoints following TMB exposure. Neurological effects are an appropriate critical adverse effect for deriving health-protective air concentrations given the consistency of these effects in studies of various duration (e.g., acute, subchronic) and considering the relatively low air concentrations at which they are observed (compared to other effects) (USEPA 2013). Lowest-observed-adverse-effect-level (LOAEL) information for the critical effect(s) in laboratory animals complements NOAEL data from human studies for derivation of the acute ReV and ESL.

Little difference in toxicity has been observed between the TMB isomers (NRC 2012). Therefore, although all available data on the individual TMB isomers were considered for acute ReV and ESL derivation, the resulting values are considered applicable to all three TMB isomers and any mixture thereof (e.g., CAS 25551-13-7).

3.1.2.1 Human Studies

No acute study human data identifying critical effects attributable to a given TMB exposure level were found by the TCEQ in the scientific peer-reviewed literature. For example, while occupational studies of workers exposed to mixtures containing TMBs for various durations (e.g., Norseth et al. 1991) have shown various neurological effects (e.g., reduced motor speed/coordination, neuropsychological effects, deficits in short-term memory, abnormal fatigue, vertigo), these studies cannot be used to identify a neurotoxicity LOAEL for any specific TMB (USEPA 2013). However, human volunteer data are useful in identifying a TMB-specific human NOAEL point of departure (POD) for the critical acute adverse effects (i.e., neurotoxicity) observed in animal studies, which provide complementary TMB-specific LOAEL values for the critical effects. As discussed below, no adverse effects (e.g., CNS/neurological, irritation) were reported in volunteers exposed up to 24 ppm for 2 h (Järnberg et al. 1996) or up to 31 ppm for 8 h (Kostrzewski et al. 1997) in pharmacokinetic studies with TMB isomers.

3.1.2.1.1 Key Human Study (Järnberg et al. 1996)

The toxicokinetics of inhaled TMBs were studied in 10 male, healthy volunteers exposed to TMB vapor in an exposure chamber for 2 h while doing light physical work (i.e., pedaling an ergometer bicycle at 50 watts). The subjects were exposed on four occasions to 24 ppm of 1,2,4-TMB, 1,2,3-TMB, or 1,3,5-TMB, or to 2 ppm of 1,2,4-TMB. There was an interval of at least 2 weeks between successive exposures. The concentration of solvent was monitored and the average chamber air concentration of TMBs was 24 ppm during high-level exposures and 2 ppm during the low-level exposure to 1,2,4-TMB. The TMB isomers were analyzed in blood, urine, and exhaled air by gas chromatography to assess the relative respiratory uptake, elimination of TMBs, volumes of distribution, half-lives of the TMBs in blood, excretion, etc. In addition, the occurrence of acute CNS-related effects and irritation was studied by means of a questionnaire. Before, during, and after exposure the subjects rated symptoms from “no effect at all” to “almost unbearable.” The administered questionnaire was comprised of irritation and CNS-related symptoms: (i) discomfort in eyes: burning, irritation, or running eyes; (ii) discomfort in nose: burning, irritation, or running nose; (iii) discomfort in throat or airways; (iv) headache; (v) fatigue; (vi) nausea; (vii) dizziness; (viii) intoxication; (ix) difficulty in breathing; and (x) smell of solvent. No irritation of the eyes, nose, throat, or airways, no CNS-related symptoms (i.e., headache, fatigue, nausea, dizziness, intoxication), and no difficulty in breathing were reported by the subjects under these exposure conditions. In regard to irritation, results of this study are consistent with the reported lack of mucous membrane irritation complaints at 35-50 ppm (Gerarde 1960 as cited in ACGIH 2001). Additionally, this study supports a free-standing, 2-h human NOAEL of 24 ppm for reported CNS-related effects due to acute TMB exposure. This 2-h human free-standing NOAEL is similar in duration to the duration of interest (1-h) and will be used, along with animal study data that identify critical effects and the exposure levels that produce them, to conservatively derive the acute ReV and ESL.

3.1.2.1.2 Supporting Human Study (Kostrzewski et al. 1997)

Although the primary goal of this study was to obtain toxicokinetic data and to investigate the relationship between biological indices of TMB exposure and absorbed dose, it also provides useful information on the potential for acute effects in humans. Inhalation tests were performed for 4 h or 8 h in an exposure chamber. The subjects were eight volunteers aged 20-39 with no history of exposure to TMBs. Volunteers were exposed to 1,2,4-TMB (9.6-154.0 mg/m^3), 1,3,5-TMB (10.2-151.1 mg/m^3), or 1,2,3-TMB (5.0-94.8 mg/m^3) at air concentrations ranging overall from 5 to 154 mg/m^3 (1 to 31 ppm). Exhaled air, capillary blood, and urine samples were collected before, during, and after exposure. The study determined: biological sample concentrations of TMBs and their metabolites, pulmonary ventilation rates, retention of TMBs in the lungs, elimination from capillary blood and urine, the relationship between biological material levels and TMB air concentration or absorbed dose, etc. In addition, routine clinical examinations were carried out before and after exposure, as well as repeatedly after the experiment in three-month intervals (additional details not provided). The study reports that there were no internal, laryngeal, hematologic, or neurologic abnormalities found during the routine

clinical examinations due to 4- and 8-h TMB exposures of up to 31 ppm. However, as opposed to Järnberg et al. (1996), this study provides no methodological details on the assessment of symptoms in exposed subjects. This study supports the 2-h human NOAEL of 24 ppm from Järnberg et al. (1996) for the lack of TMB-induced acute effects (e.g., CNS/neurological, irritation), which will be discussed below in the context of the critical adverse effects (i.e., neurotoxicity) observed and identified in animal studies.

3.1.2.2 Animal Studies

Effects on the nervous system (e.g., neurotoxicity such as decreased motor coordination and pain sensitivity) are the most widely observed adverse effects in animals (USEPA 2013).

3.1.2.2.1 Key Animal Study (Korsak and Rydzynski 1996)

The rat study of Korsak and Rydzynski (1996) provides information on the critical effects of acute TMB exposures (i.e., the neurotoxic effects at the lowest LOAELs). This study examined the neurobehavioral effects of acute exposure to 1,2,3-, 1,2,4-, or 1,3,5-TMB in male Wistar rats. Ten rats per group were exposed for 4 h to 0 ppm (sham control) or to 250-2,000 ppm (1,230-9,840 mg/m^3) in one of 4 to 5 TMB-exposed groups (apparent nominal concentrations, more specific analytical concentrations not reported although measured every 30 minutes by gas chromatograph with a flame-ionization detector). Rotarod performance (in adequately trained animals) was tested for each exposure group before and immediately after exposure. Rotarod performance is the ability of rats to remain on an 8-cm diameter rotating rod (12 rpm) for 2 minutes and is an index of neuromuscular (motor coordination) function. Hot-plate behavior was also tested in all groups immediately following termination of exposure. Hot-plate behavior is a measure of pain sensitivity (in this case, decreased pain sensitivity or analgesia) and is recorded as the latency (increase in seconds, expressed as percent increase) of the paw-lick response following the placement of the rat on a hot plate (NCEA 2010, Korsak and Rydzynski 1996).

No mortalities were noted by the study authors. Acute exposure to the three TMB isomers induced concentration-dependent decreases in rotarod performance and pain sensitivity. The study authors identified 1,2,3-TMB as the isomer producing the most pronounced neurotoxic effects, although results for 1,2,4- and 1,3,5-TMB were similar. For 1,2,3-TMB, the acute EC_{50} (effective concentration median or EC_{50}) for impaired rotarod performance was calculated to be 768 ppm (3,779 mg/m^3), with 95% confidence intervals of 578-942 ppm (2,832-4,615 mg/m^3). The acute EC_{50} for the hot-plate test (concentration that increased the latency of the paw-lick response to 50% over control) for this isomer was calculated to be 848 ppm (4,155 mg/m^3), with 95% confidence intervals of 694-982 ppm (3,400-4,811 mg/m^3). These EC_{50} values for measures of neurotoxicity were lower for 1,2,3-TMB by 24-43% compared to those for 1,2,4- and 1,3,5-TMB. Consequently, the study authors identified this isomer as the most acutely neurotoxic TMB isomer, and the TCEQ focused the evaluation below on 1,2,3-TMB.

The specific numerical data for 1,2,3-TMB are not available for benchmark dose (BMD) modeling, which could estimate an effect level lower than the EC_{50} value (e.g., the benchmark

concentration corresponding to the 10% response level (BMC_{10}) or the 95% lower confidence limit ($BMCL_{10}$)). However, results are presented graphically for 1,2,3-TMB (hemimellitene) at the bottom of Figures 1 and 2 in Korsak and Rydzynski (1996). The EC_{50} value for impaired rotarod performance (768 ppm) due to 1,2,3-TMB exposure shown in Figure 1 of the study is somewhat lower than that for increased latency in the hot-plate test (848 ppm) shown in Figure 2 of the study. While EC_{50} values may be appropriate to compare the relative toxicities of different chemicals or isomers, they are generally not appropriate for use as a POD by the TCEQ for derivation of a health-protective concentration for everyday public exposure to ambient air as the associated response rate is too high (e.g., 50% response rate for impaired rotarod performance). Examination of the least squares regression line (i.e., dose-response line) for 1,2,3-TMB at the bottom of Figure 2 of the study shows that there was 0% increased latency in the hot-plate test at a tested concentration between 2,000 and 3,000 mg/m^3, estimated by the TCEQ at approximately 2,400 mg/m^3 (489 ppm). Thus, the NOAEL for decreases in pain sensitivity due to 4-h 1,2,3-TMB exposure is considered to be 2,400 mg/m^3 (489 ppm).

Although BMD modeling cannot be conducted for impaired rotarod performance, the regression line shown for 1,2,3-TMB (hemimellitene) in Figure 1 of the study can be used to estimate the response (i.e., percent failure as a measure of impaired test performance due to neurotoxicity) at various 4-h exposure concentrations. To demonstrate this, Figure 1 below closely approximates the original study figure:

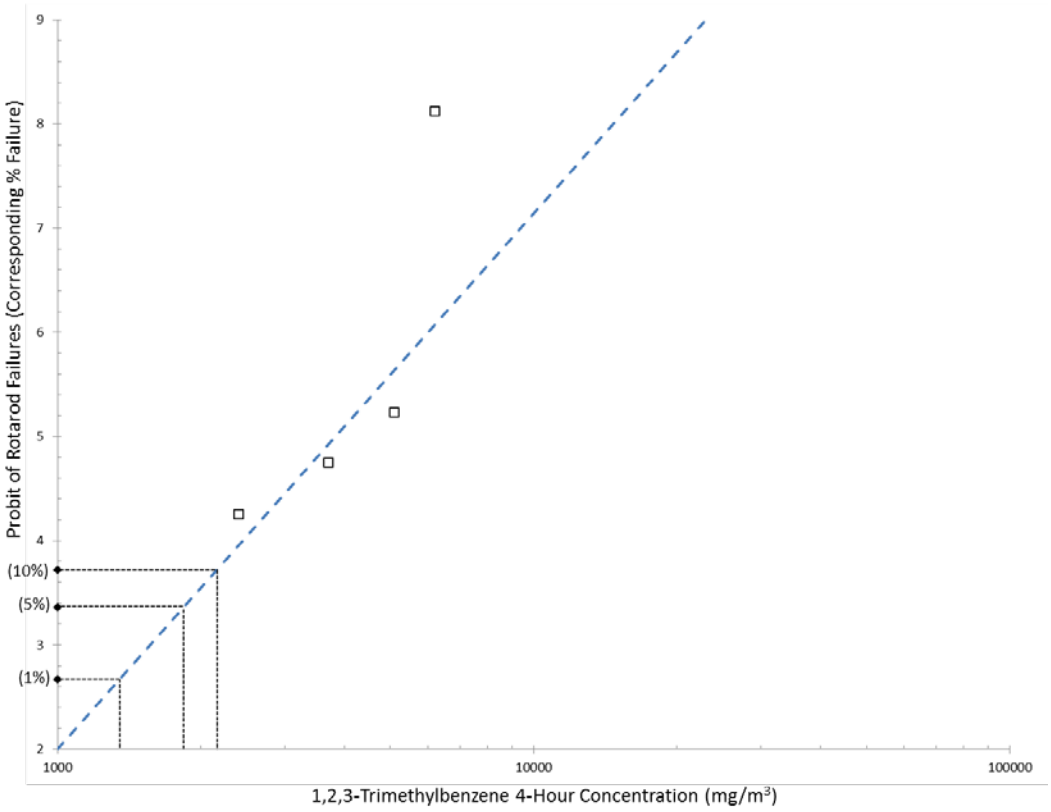


Figure 1: Rotarod Performance in Rats Exposed to 1,2,3-TMB

While the x-axis of the figure is dose (mg/m^3), the y-axis is the probit (unit of measurement of statistical probability based on deviations from the mean of a normal distribution) of failures and corresponds to the percentage of failures for each exposure group expressed as the corresponding probit value. For example, a probit of 3.72 on the y-axis corresponds to a 10% response rate (an EC_{10} for failure on the rotarod test in this case). A 10% response rate is often used for BMD analysis and is not far below the range of the data (i.e., the lowest study data point appears to be associated with a probit just over 4, around a 20% response). Based on the regression line shown for 1,2,3-TMB at the bottom of Figure 1 of the study (closely approximated in Figure 1 above) and estimated to the nearest hundred mg/m^3, the 4-h air concentration associated with a 10% response (probit of 3.72) would be greater than 2,000 mg/m^3, approximately 2,200 mg/m^3 (447 ppm). Since a lower bound cannot be calculated for the air concentration corresponding to a 10% response (i.e., the EC_{10}), the TCEQ also estimated the air concentration corresponding to a response rate of 5% (i.e., an EC_{05}). These PODs (corresponding to responses of 5 and 10%) may be conservative as they do not account for the failure rate in controls (not reported) and thus inherently assume 0% failure in controls for the rotarod test (i.e., they correspond to total risk of failure as opposed to extra risk of failure due to 1,2,3-TMB). Based on the regression line shown for 1,2,3-TMB (hemimellitene) in Figure 1 of the study, the estimated air concentration

associated with a response of 5% (probit of 3.36) would be approximately 1,800 mg/m^3 (366 ppm).

As these air concentrations (corresponding to responses of 5 and 10%) are lower than the NOAEL for decreases in pain sensitivity induced by 1,2,3-TMB (≈ 2,400 mg/m^3 or 489 ppm), the TCEQ used impaired rotarod performance as the most sensitive (i.e., critical) neurotoxic effect. Furthermore, these 4-h air concentrations of 366 and 447 ppm corresponding to responses of 5 and 10% for the most sensitive neurotoxicity study endpoint (i.e., impaired rotarod performance) demonstrate the free-standing, 2-h human NOAEL of 24 ppm for CNS/neurological and irritation effects (Järnberg et al. 1996) to be conservative. In fact, even the 4-h air concentration of 264 ppm (1,300 mg/m^3) estimated at a response level of 1% (probit of 2.67), well below the range of the data and unadjusted for any rotarod failures in the controls, is over ten-fold higher than the 2-h NOAEL being used by the TCEQ for derivation of the acute ReV and ESL. Thus, considering human data (e.g., the absence of acute effects in human exposure chamber studies) and the critical effect identified in laboratory animal studies (i.e., neurotoxicity), the 2-h human NOAEL of 24 ppm will conservatively be used as the POD for development of the acute ReV and ESL. That is, the 2-h human free-standing NOAEL (24 ppm) for TMB isomers will be used to derive the acute ReV and ESL, with the 4-h air concentration associated with a 10% response (447 ppm) identifying the neurotoxic critical effect (i.e., impaired rotarod performance in rats).

3.1.2.2.2 Supporting Animal Studies

The supporting animal studies discussed below (taken from NRC 2012) are useful as additional supporting information in the derivation of the acute ReV and ESL.

- In Cameron et al. (1938), male and female Wistar rats (number per sex not specified) and mice (strain and number per sex not specified) were exposed in whole body inhalation chambers to 1,2,4- or 1,3,5-TMB. Atmospheres were generated by bubbling air through a saturation unit, and the chamber atmospheres were described as being accurate during a continuous run. No adverse clinical signs, deaths, or necropsy findings occurred in rats (n = 4-8) exposed to 1,2,4-TMB at 1,800-2,000 ppm for up to 48 h, or for 8 h/day for 14 days. No animals died in groups (n = 10) exposed at 560 ppm for 24 h, or for 8 h/day for 14 days. Four of 16 rats exposed continuously to 1,3,5-TMB at 2,240 ppm for 24 h died (narcosis developed and the animals died of respiratory failure, with pulmonary congestion being observed at necropsy). In mice, no adverse clinical signs, deaths, or necropsy findings occurred in animals (n = 10) exposed to 1,3,5-TMB at 560 ppm for 24 h, or for 8 h/day for 14 days. Likewise, no effects were seen in mice (n = 10) exposed to 1,2,4-TMB at 1,800-2,000 ppm for 12 h. The absence of adverse clinical signs and necropsy findings in mice and rats exposed to 560-2,000 ppm of 1,3,5- or 1,2,4-TMB for 12 to 48 h supports use of the 2-h human POD (NOAEL of 24 ppm) being used for the more sensitive effect of TMB-induced neurotoxicity (e.g., the 4-h air concentration of

1,2,3-TMB associated with a 10% response for neurotoxicity (impaired rotarod performance) in rats is 447 ppm).

- In Wiglusz et al. (1975a,b), groups of six male Wistar rats were exposed to 1,3,5-TMB at 0, 61, 305, 609, or 1,218 ppm for 6 h. No details were provided on the purity of 1,3,5-TMB, exposure apparatus, atmosphere generation, or monitoring. Blood was collected at various times after exposure for analyses of hematology and serum enzyme activity. No changes were found in hemoglobin concentration, erythrocyte and leukocyte count, or the activity of aspartate aminotransferase, alanine amino transferase, or glutamate dehydrogenase. An insignificant slight increase in the percentage of segmented neutrophils and an insignificant slight reduction in the percentage of lymphocytes were observed immediately after exposure, and alkaline phosphatase activity was higher on day 7 post exposure for the 609 ppm group only (a dose-response was absent). Clinical findings and body weight were not mentioned. The absence of significant, dose-related adverse hematological effects in this study for rats exposed up to 1,218 ppm 1,3,5-TMB for 6 h supports use of the 2-h human POD (NOAEL of 24 ppm) being used for the more sensitive effect of TMB-induced neurotoxicity.

- Lastly, Lazarew (1929) exposed white mice (strain and number per sex not specified) to 1,2,4- or 1,3,5-TMB in whole body inhalation chambers for 2 h. Details of atmosphere generation were not provided. Mice exposed to 1,2,4-TMB at 8,100 ppm or to 1,3,5-TMB at 5,000-7,000 ppm exhibited lateral position during exposure. Slightly higher concentrations of 8,100-9,100 ppm and 7,000-9,000 ppm for 1,2,4- and 1,3,5-TMB, respectively, resulted in loss of reflexes. The high effect levels observed in this study (e.g., > 5,000 ppm 1,3,5-TMB) support use of the 2-h human POD (NOAEL of 24 ppm) being used for the more sensitive effect of TMB-induced neurotoxicity (e.g., the 4-h air concentration of 1,2,3-TMB associated with a 10% response for neurotoxicity (impaired rotarod performance) in rats is 447 ppm).

Collectively, these animal studies support use of TMB-induced neurotoxicity as the critical effect for derivation of the acute ReV and ESL.

3.1.2.3 Developmental and Reproductive Studies

NRC (2012) contains a summary of data relevant to the potential developmental and reproductive effects of TMBs. The results reported elsewhere for other studies were also considered (e.g., no neurological effects reported in the offspring of rats exposed 24-h/day to ≥ 600 mg/m^3 C9 aromatics on gestation days 7-15 in Lehotzky et al. 1985). The following was taken (much of it verbatim) from NRC (2012):

Female Sprague-Dawley rats (n = 24) were exposed whole body to 1,3,5-TMB at 100-1,200 ppm or to 1,2,4-TMB at 100-900 ppm (purity was 99% for both isomers) for 6 h/day on gestation days 6-20 (Saillenfait et al. 2005). Atmospheres were monitored by a gas chromatograph

equipped with a flame-ionization detector. Mean measured concentrations differed by less than 2% of nominal concentrations. Maternal toxicity was evident as decreased body weight gain and reduced food consumption with 1,3,5-TMB at concentrations of 300 ppm and greater and with 1,2,4-TMB at concentrations of 600 ppm and greater. All dams survived, and no clinical signs of toxicity were observed. Fetal body weight was decreased with both isomers at concentrations of 600 ppm and greater. No external, visceral, or skeletal malformations were observed with either isomer. The TCEQ notes that the maternal LOAELs for decreased body weight gain and reduced food consumption due to subacute (i.e., 15-day) exposure are 300-600 ppm, and that these maternal effects are associated with decreased fetal weight at ≥ 600 ppm. Furthermore, the TCEQ concurs with USEPA (2013) that due to the similarity in toxicity of the three TMB isomers, this study fulfills the developmental study portion of the toxicity database for 1,2,3-TMB and that a developmental POD lower than that for 1,2,3-TMB-induced neurotoxicity (the basis for the acute ReV and ESL) in adult animals is unlikely.

In McKee et al. (1990), groups of 30 female CD-1 mice (confirmed to have mated) were exposed whole body to C9 aromatic hydrocarbons at target concentrations of 0, 100, 500, or 1,500 ppm for 6 h/day on gestation days 6-15 (IRDC 1988, McKee et al. 1990). Mean analytically-determined exposure concentrations based on hourly measurements during the study were 102, 500, and 1,514 ppm, respectively. The composition of the test material contained 55.1% TMBs (8.37% 1,3,5-TMB, 40.5% 1,2,4-TMB, 6.18% 1,2,3-TMB). The remainder of the mixture was comprised of o-xylene, cumene, n-propyl benzene, and 4-, 3-, and 2-ethyltoluene. Due to the presence and similarity (e.g., structural, metabolic, toxicological) of other C9 alkylbenzenes (e.g., ethyltoluenes, cumene), TCEQ cannot assume that the TMBs alone are responsible for the effects observed. Rather, the cumulative effect of exposure and the total C9 exposure concentration is considered the most relevant dose metric (e.g., xylenes, cumene, and toluene can also cause neurotoxicity). No treatment-related mortality, clinical signs of toxicity, or changes in food consumption were observed at 102 or 500 ppm. A total of 12 animals exposed at 1,514 ppm died between gestation days 8-16. Clinical signs of toxicity at 1,514 ppm included abnormal gait (18 animals), labored breathing (9), hunched posture (9), weakness (7), inadequate grooming (7), circling (8), and ataxia (8). Most of these signs were observed after one or two days of exposure. Maternal body weight gain by the 500 and 1,514 ppm groups was statistically significantly decreased on gestation days 6-15 and gestation days 0-18 compared to the control group. Maternal body weight gain in the 102 ppm group was similar to the 500 ppm group, but was not statistically significant. Effects on maternal body weight were inconsistent, with non-monotonic decreases across exposure groups on gestation day15 while on gestation day 18, body weight was only significantly decreased for the 1,514 ppm exposure group. Food consumption by the 1,514 ppm group was 65-77% of the control group. Hematologic analyses on gestation day 15 revealed significantly reduced hematocrit and mean corpuscular volume and increased mean corpuscular hemoglobin concentration in mice exposed at 1,514 ppm compared with controls. Maternal necropsy was unremarkable. On gestation day 18, dams in the 1,514 ppm group had significantly fewer live fetuses/dam because of an increase in post-implantation loss compared with controls. Although the number of live fetuses/dam was also reduced in the 102 ppm group,

the authors note that this reduction was not dose-related as it did not occur in the 500 ppm exposure group. Additionally, neither the number of implantations/dam nor the number of post-implantation losses/dam was significantly affected at 102 or 500 ppm. Fetal body weight in the mid- and high-concentration groups (500 and 1,514 ppm), but not in the low-concentration group (102 ppm), was significantly reduced compared to that of controls (1.16 and 0.82 g, respectively, vs. 1.25 g for controls). Cleft palate was found in 14 fetuses from seven high-concentration (1,514 ppm) litters compared with one control fetus, which the study authors suggest may have been secondary to maternal toxicity, and reduced ossification of the skull was found in 18 fetuses from six high-concentration litters compared with none in the controls. The TCEQ notes that the maternal LOAEL for decreased body weight gain due to subacute (i.e., 10-day) exposure is 500 ppm, and that this maternal effect at 500 and 1,514 ppm is associated with decreased fetal weight at the same exposure concentrations.

While the TCEQ agrees with USEPA (2013) that individual TMB isomer studies are preferable for deriving toxicity factors specific to TMBs, relevant data (e.g., that address a potential data gap) should not be ignored because they are not ideal for this narrow purpose. While C9 aromatic hydrocarbon data are not amenable to deriving TMB-specific toxicity factors (e.g., conducting dose-response assessments of individual isomers), the consideration of several factors suggests that they are nevertheless relevant to the potential of TMBs to cause developmental/reproductive effects:

(1) In the study discussed above (McKee et al. 1990), TMBs comprised the majority of the C9 fraction to which animals were exposed.

(2) Exposure to the significant (i.e., majority) fraction of TMBs present as part of the C9 fraction appears more representative of typical public exposure than individual TMBs as “vehicle emissions are expected to be the major anthropogenic source of TMBs” due to the widespread use of the C9 fraction as a component of gasoline (USEPA 2012). This consideration mitigates concern about some potential difference in toxicity between a TMB mixture study and individual TMB isomer study as routine public exposure may be expected to be to a TMB mixture as part of the C9 component in gasoline (note that this DSD applies the most conservative values to TMB mixtures in addition to the individual isomers).

(3) Use of these data (at least in a limited way) may be viewed as consistent with USEPA (2000), which suggests using available mixture toxicity data for mixtures of concern. This consideration applies here to the extent that C9 fraction-associated vehicle emissions are expected to be the major anthropogenic source of exposure to TMBs, although this DSD does not derive toxicity factors specifically for this fraction but for TMBs which could be emitted (alone or as part of a mixture) from any source. However, the goal of deriving TMB-specific toxicity factors, in the absence of other more specific and arguably more relevant or complementary data, does not justify disregarding data relevant and informative as to the potential of TMBs to cause effects of

potential concern (e.g., developmental/reproductive) despite that the data cannot be used directly to derive the specific toxicity factors desired.

(4) Lastly, USEPA (2013) acknowledges in Appendix E that the study included above (McKee et al. 1990) is exceptional among C9 fraction studies in that it clearly observed developmental and reproductive toxicity.

Collectively, these considerations suggest that these C9 fraction data are largely relevant and informative here but that the toxicity factors in this DSD should be TMB specific. More specifically, without having to serve as surrogate data for any specific isomer, these C9 data enhance the database in regard to the types of developmental/reproductive effects that TMBs may cause and provide an indication of how the levels producing such effects compare to those of specific TMB isomers producing neurological effects.

Decreased fetal weight in the studies described above being associated with decreased maternal body weight (i.e., decreased fetal weight secondary to maternal toxicity) suggests that protecting dams from this subacute adverse effect will also protect the fetus. Additionally, the TCEQ notes that developmental/reproductive effects (i.e., cleft palate, reduced ossification, post-implantation loss with reduced live fetuses/dam) and maternal clinical signs of clinical toxicity (e.g., abnormal gait, weakness, ataxia) occurred at a subacute exposure concentration of 1,514 ppm, which is 63-fold higher than the 2-h human POD (24 ppm) being used to calculate the 1-h acute ReV, over 3-fold higher than the estimated EC_{10} (447 ppm) for 1,2,3-TMB-induced neurotoxicity (i.e., failure on the rotarod test) in the Korsak and Rydzynski (1996) rat study, and even exceeds the cited EC_{50} values (768 and 848 ppm) for both measures of neurotoxicity (i.e., failure on the rotarod test, decreased pain sensitivity in the hot-plate test) for the most acutely neurotoxic TMB isomer in that study (1,2,3-TMB).

Thus, consistent with USEPA (2013), the TCEQ concludes that TMB exposure levels that elicit these types of effects (e.g., on pregnant animals and developing fetuses) are greater than those that cause effects on the nervous system (i.e., neurotoxicity is a more sensitive endpoint). This information suggests that protecting against potential neurotoxicity as the critical acute adverse effect will also protect against potential developmental/reproductive effects.

3.1.3 Mode-of-Action (MOA) Analysis

Little is known about the mechanism of TMB toxicity (NRC 2012). TMB isomers have been reported to metabolize to various metabolites, including benzoic and hippuric acid metabolites, mercapturic acids, phenols, and glucuronides and sulphuric acid conjugates (USEPA 2013). USEPA (2013) contains a discussion of possible MOAs for TMB-induced neurological effects (see pages 1-19 to 1-20), which are hypothesized to include (but are not limited to):

- Changes in the concentration and turnover rate of dopamine and norepinephrine in various regions of the rat brain due to potential metabolites with an affinity to

catecholamine receptors that would, in turn, influence the uptake and release of neurotransmitters;

- Perturbation of the phospholipids on the nerve cell membrane indirectly affecting the binding of neurotransmitters to the catecholamine or other receptors and potentially leading to alterations in receptor activity or uptake-release mechanisms;

- Interaction with the neuronal receptors (e.g., catecholaminergic systems, ion channels) followed by, at much higher exposures, interaction with the lipid membrane when the available sites on the neuronal receptors are completely occupied.

Ultimately, although the neurotoxicity observed following acute exposure (and subchronic exposure) may indicate that TMBs perturb normal neurotransmission in exposed animals, the specific key events necessary for TMB-induced neurotoxicity are not established (USEPA 2012).

3.1.4 Point of Departure (POD) for Key Study and Critical Effect

A free-standing, 2-h human NOAEL of 24 ppm from the Järnberg et al. (1996) study, for the critical effect of neurotoxicity (e.g., CNS/neurological effects, impaired rotarod performance as a measure of motor coordination, balance, and overall neuromuscular system function) as established by Korsak and Rydzynski (1996), will be used as the POD.

3.1.5 Dosimetric Adjustments

Duration adjustments from a longer to shorter duration are not conducted for a free-standing NOAEL used as the POD when no other data are available, that is, when there are no dose-response data to inform the slope of the dose-response relationship (TCEQ 2015a). However, in this case there are sufficient animal dose-response data to show that the duration adjusted POD falls well below levels associated with the most sensitive adverse effects of TMB. Accordingly, the 2-h duration free-standing NOAEL/POD (C_1) from Järnberg et al. (1996) was duration adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity:

$$\begin{aligned} C_2 &= [(C_1)^3 \times (T_1 / T_2)]^{1/3} \\ &= [(24\ \text{ppm})^3 \times (2\ \text{h}/1\ \text{h})]^{1/3} \\ &= 30.2\ \text{ppm}\ (148.6\ \text{mg/m}^3) = POD_{ADJ} \end{aligned}$$

This adjustment is consistent with available data which indicate that duration plays a role in neurotoxicity. For example, for 4-h exposure to 1,2,3-TMB (hemimellitene), Figure 1 of Korsak and Rydzynski (1996) shows that around a 40% failure in the rotarod test (probit of 4.75) occurred at a 4-h air concentration of approximately 3,700 mg/m^3 (consistent with the EC_{50} of 3,779 mg/m^3). By contrast, examination of Figure 3 of the study shows that exposure to 1,230

mg/m^3 1,2,3-TMB was all that was required to produce the same 40% failure at 4 weeks, which by week 13 had produced a rotarod failure response of approximately 70%. These and other data demonstrate that in addition to concentration, duration plays a role in toxicity.

As the POD_{ADJ} is based on human data, the human equivalent concentration POD_{HEC} is the same value of 30.2 ppm (148.6 mg/m^3).

3.1.6 Adjustments of the POD_{HEC} and Application of Uncertainty Factors

The POD_{HEC} is based on neurological effects, which are threshold in nature. The default for threshold effects is to determine a POD_{HEC} and apply uncertainty factors (UFs) to derive an acute ReV (i.e., assume a threshold MOA) (TCEQ 2015a). The following UFs were applied to the POD_{HEC} of 30.2 ppm (148.6 mg/m^3) (duration-adjusted NOAEL): 10 for potential intrahuman variability (UF_H), and 1 for database deficiency (UF_D); total UF =10.

- An UF_H of 10 was considered appropriate to account for potential intrahuman variability.

- An UF_D of 1 was used since there are informative acute inhalation studies in humans and two laboratory animal species (i.e., Wistar rats, Balb/c and other mice), as well as relevant developmental/reproductive study information in two animal species (i.e., Sprague-Dawley rats, CD-1 mice). Thus, acute database confidence is considered high (TCEQ 2015a).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D)$$
$$= 30.2 \text{ ppm} / (10 \times 1)$$
$$= 30.2 \text{ ppm} / 10$$
$$= 3 \text{ ppm or } 15 \text{ mg/m}^3 \text{ (rounded to two significant digits)}$$

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

In deriving the acute ReV for 1,2,3-TMB, which will be used for other isomers as well, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The resulting 1-h acute ReV is 3 ppm (15 mg/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 0.9 ppm (4.4 mg/m^3) (Table 4).

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

Parameter	Values and Descriptions
Study	Järnberg et al. (1996)
Study Population	10 male volunteers doing light physical work
Study Quality	Medium-high
Exposure Concentrations	24 ppm 1,2,3-, 1,2,4-, or 1,3,5-TMB
Exposure Duration	2 h on four occasions (≥ two weeks apart)
POD (2 h)	24 ppm (118 mg/m^3) (free-standing NOAEL)
Critical Effects	Neurotoxicity (i.e., impaired rotarod performance as established by Korsak and Rydzynski 1996) in rats
Extrapolation from 4 h to 1 h	Haber's rule with n=3
POD_{ADJ} (1 h)	30.2 ppm (148.6 mg/m^3)
POD_{HEC}	30.2 ppm (148.6 mg/m^3)
Total UF	10
Intraspecies UF	10
Incomplete Database UF *Database Quality*	1 High
acute ReV [1 h] (HQ = 1)	**15 mg/m^3 or 15,000 µg/m^3 (3,000 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**4.4 mg/m^3 or 4,400 µg/m^3 (900 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

TMBs have a strong, pleasant aromatic odor (USEPA 2013, ACGIH 2001). Based on TCEQ (2015b), an odor-based value was not derived.

3.2.2 Vegetation Effects

After a literature review, there were no data found on any adverse effects of TMBs on vegetation.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

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

- ^{acute}ESL = 4,400 µg/m^3 (900 ppb)
- acute ReV = 15,000 µg/m^3 (3,000 ppb)

The short-term ESL for air permit evaluations is the ^{acute}ESL of 4,400 µg/m^3 (900 ppb). The acute ReV of 15,000 µg/m^3 (3,000 ppb) may be used for the evaluation of ambient air monitoring data (Table 1). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.4 Acute Inhalation Observed Adverse Effect Level

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 observed adverse effects levels in DSDs (TCEQ 2015a). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. Regarding critical effects due to acute TMB exposure, the animal study of Korsak and Rydzynski (1996) provides an approximate 4-h EC_{10} of 2,200 mg/m^3 for neurotoxicity (i.e., impaired rotarod performance). This animal EC_{10} was used as the animal acute inhalation observed adverse effect level for extrapolation to humans. No duration adjustment was made (TCEQ 2015a).

In the acute exposure portion of Korsak and Rydzynski (1996), 1,2,3-TMB acted as a Category 3 vapor, producing a systemic effect as the critical adverse effect (i.e., neurotoxicity). The default pharmacokinetic animal-to-human dosimetric adjustment for a Category 3 vapor is multiplication of the animal-based POD by the ratio of the animal/human blood:gas partition coefficients (TCEQ 2015a):

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

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

Blood:air partition coefficients for 1,2,3-TMB have been reported for humans and rats in Meulenberg and Vijverberg (2000). The reported partition coefficients of 66.5 (human) and 62.6 (rat) for 1,2,3-TMB are used in calculation of the POD_{HEC}:

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 2{,}200 \text{ mg/m}^3 \times 62.6/66.5 = 2{,}071 \text{ mg/m}^3 \text{ (421 ppm)}$$

Thus, following animal-to-human dosimetric adjustment, the 4-h $EC_{10\text{-}HEC}$ based on this study is estimated to be 2,071 mg/m^3 (421 ppm). The $EC_{10\text{-}HEC}$ 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 study (4 h) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences

in sensitivity. The acute inhalation observed adverse effect level of 2,071 mg/m^3 (421 ppm) is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the estimated 4-h acute inhalation observed adverse effect level of 2,071 mg/m^3 (421 ppm) and the 1-h acute ReV of 15 mg/m^3 is a factor of 138.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Toxicological profiles of TMBs such as USEPA (2013), NCEA (2007, 2009, 2010), and ACGIH (2001) were reviewed for this section along with conducting a literature review for more current studies. Ultimately, due to inadequate human data, a subchronic laboratory animal study (Korsak and Rydzynski 1996) was selected as the key study to derive the chronic ReV and ESL.

Consistent with the acute evaluation (Section 3.1), as little difference in toxicity has been observed between the TMB isomers (NRC 2012), although all available data on the individual TMB isomers were considered, the resulting chronic ReV and ESL values are considered applicable to all three TMB isomers and any mixture thereof.

4.1.1 Physical/Chemical Properties

The primary physical and chemical properties of TMBs are discussed in Chapter 3 and summarized in Table 3.

4.1.2 Key and Supporting Studies

4.1.2.1 Human Studies

Occupational and residential exposure studies have reported health effects (e.g., neurological, eye irritation). However, these studies involved exposures to mixtures of TMBs and other volatile organic compounds, so accurately ascertaining the contribution of TMBs to the reported toxic effects would be problematic (USEPA 2013). Consequently, these studies cannot be used as the basis to derive the TMB-specific toxicity factors for this DSD (i.e., toxicity factors based on effects induced specifically by TMBs alone). TMB isomer animal studies (e.g., Korsak and Rydzynski 1996) are available for this purpose and provide LOAELs and POD values for TMB-specific effects. Due to the lack of sufficient human data, an animal study was used to develop the chronic ReV and ESL.

4.1.2.2 Animal Studies

Since neither adequate human toxicity data nor chronic animal data are available, the TCEQ will utilize a subchronic animal study to develop the chronic ReV and ESL. The USEPA recently reviewed the available scientific literature on TMBs (USEPA 2013). The TCEQ agrees that the subchronic inhalation studies available indicate disturbances in CNS function (e.g., neurotoxicity

such as decreased pain sensitivity and decreased neuromuscular function and coordination) to be the most sensitive adverse effects due to TMB exposure. More specifically, decreased pain sensitivity has been observed in multiple studies of different durations (e.g., acute, short-term, subchronic) and was selected by USEPA as the critical effect, with Korsak and Rydzynski (1996) being selected as the key study for derivation of the draft reference concentration (RfC). The TCEQ agrees with these critical effect and key study selections. See USEPA (2013) for detailed discussions of the other studies and endpoints considered.

4.1.2.2.1 Key Animal Study

The Korsak and Rydzynski (1996) rat study was peer reviewed and well designed, utilizing three dose groups, untreated controls, and a satisfactory number of animals per dose group for assessing neurotoxicity following subchronic exposure to TMBs (USEPA 2013). The TCEQ concurs with this study and endpoint selection based on review of the relevant literature (e.g., a scientific literature search did not identify a more recent and appropriate study). Accordingly, the TCEQ will utilize the subchronic rat study of Korsak and Rydzynski (1996) as the key study for derivation of the chronic ReV and ESL (this study also provided information on the acute neurotoxic effects of TMBs, which will not be repeated here; see Section 3.1.2.2.1). The following summary of Korsak and Rydzynski (1996) was taken almost verbatim from NCEA (2010, 2007):

Korsak and Rydzynski (1996) examined the neurobehavioral effects of subchronic exposure to 1,2,3-TMB (hemimellitene) and 1,2,4-TMB (pseudocumene) in male Wistar rats of IMP:DAK outbred stock. Animals were exposed (10 per group) at concentrations of 0 ppm (sham control), 25 ppm (123 mg/m^3), 100 ppm (492 mg/m^3), or 250 ppm (1,230 mg/m^3) in a dynamic inhalation chamber for 6 h/day, 5 days/week, for 3 months. Concentrations in the inhalation chamber were measured every 30 minutes using a gas chromatograph with a flame-ionization detector. Animals were observed for clinical signs during the course of the study. Body weights were measured at the beginning and end of the study. Food and water consumption were not measured. Rotarod performance was tested on each group (10 per group) prior to the start of the study, weekly during the experiment and 2 weeks following exposure termination (1,230 mg/m^3 group only). Rotarod performance, an index of neuromuscular function, tested the ability of the rats to remain on a rotating rod for 2 minutes. Hot-plate behavior was tested in all groups immediately following termination of exposure and 2 weeks after exposure (1,230 mg/m^3 group only) of the paw-lick response following the placement of the rat on a hot plate. The study authors reported no mortalities during the study. No remarkable clinical signs or significant changes in final body weights were observed in any group.

Exposure to 1,2,3-TMB was associated with time- and dose-dependent decreases in both rotarod performance and pain sensitivity. The rotarod data were reported graphically; only the results for the testing conducted at study initiation (control), 4 and 8 weeks following study initiation, exposure termination at week 13, and 2 weeks following exposure termination were presented.

Changes in rotarod performance (increased percent of failures compared with the control) were reported to be statistically significant ($p < 0.005$) in the 492 mg/m^3 group at study termination (week 13), and in the 1,230 mg/m^3 group at 4 and 8 weeks following study initiation, at exposure termination (week 13), and 2 weeks following exposure termination (week 15). The study authors observed no statistically significant changes in rotarod performance in the 123 mg/m^3 1,2,3-TMB group. The hot-plate behavior data were reported in tabular form. Changes in hot-plate behavior (increased latency of the paw-lick response compared with the control) were reported to be statistically significant ($p < 0.05$) at study termination in all treatment groups. The mean latency of the paw-lick response, when compared with the control group, was increased by 22%, 68%, and 78% in the 123, 492, and 1,230 mg/m^3 1,2,3-TMB groups, respectively. Partial recovery in behavior (13% increase in latency compared with the control) was observed 2 weeks after cessation of exposure. Based on an increased latency of the paw-lick response, the study identifies a subchronic LOAEL of 123 mg/m^3 (25 ppm) for 1,2,3-TMB-induced neurological impairment (i.e., decreased pain sensitivity).

For 1,2,4-TMB, exposure-related indicators of neurotoxicity were also noted. Rotarod performance failure increased in a concentration-related manner, but reached the level of statistical significance (40% failure; $p < 0.05$) only in the highest (1,230 mg/m^3) exposure group following 8 or 13 weeks of exposure. Although the mean rotarod performance failure rate in the highest exposure group remained at 30% after a 2-week recovery period, the rate was not significantly different from controls. Pain-sensitivity was also decreased in a concentration-dependent manner (as evidenced by increased latency of the paw-lick response). Increased latency of the paw-lick response reached the level of statistical significance in the 492 and 1,230 mg/m^3 1,2,4-TMB groups. The mean latency of the paw-lick response, when compared with the control group, was increased by 18%, 79%, and 95% in the 123, 492, and 1,230 mg/m^3 1,2,4-TMB groups, respectively. After a 2-week recovery period, the highest (1,230 mg/m^3) exposure group no longer exhibited a significant difference in pain sensitivity, relative to controls. This subchronic study identifies a NOAEL of 123 mg/m^3 (25 ppm) and a LOAEL of 492 mg/m^3 (100 ppm) for 1,2,4-TMB-induced neurological impairment (i.e., decreased pain sensitivity).

Thus, Korsak and Rydzynski (1996) provides subchronic study LOAELs of 123 and 492 mg/m^3 (25 and 100 ppm) for 1,2,3- and 1,2,4-TMB-induced neurotoxicity (i.e., decreased pain sensitivity), respectively, with a study NOAEL of 123 mg/m^3 (25 ppm) for 1,2,4-TMB. The BMD modeling and physiologically-based pharmacokinetic (PBPK) modeling conducted for this study by USEPA (2013) for identification of PODs is briefly discussed below in Section 4.1.5.

4.1.2.2.2 Supporting Animal Studies

As mentioned above, the USEPA recently reviewed the available scientific literature on TMBs and identified neurotoxicity (e.g., decreased pain sensitivity) to be the most sensitive adverse effect due to TMB exposure. In doing so, USEPA (2013) conducted numerous evaluations and dose-response assessments of other endpoints (e.g., inflammatory lung lesions, effects on cells in bronchoalveolar lavage fluid, decreased red blood cells, decreased clotting time, neutrophil

effects, increased white blood cells, decreased reticulocytes, decreased fetal weight and maternal weight gain) based on other animal TMB isomer studies which need not be discussed again here. The TCEQ notes that none of the POD_{HEC} values for these numerous endpoints were lower than that based on neurotoxicity/decreased pain sensitivity and several (e.g., decreased fetal weight and maternal weight gain) were significantly higher (e.g., Tables 2-3, 2-8, and 2-13 of USEPA 2013). Please refer to USEPA (2013) for additional information on the analyses conducted for supporting animal studies.

Laboratory animal studies not utilized in USEPA (2013) involving exposures to mixtures of TMBs and other volatile organic compounds (e.g., C9 fraction exposure in Douglas et al. 1993, Clark et al. 1989) were also reviewed by the TCEQ for relevant information (e.g., the potential for neurological effects, inhalation toxicity, and associated effect levels). While these well-conducted studies are relevant to the potential of TMBs to cause adverse effects and would provide critical information in the absence of studies specifically evaluating TMB isomers (e.g., as is the case for reproductive effects), they cannot be used to derive the TMB-specific toxicity factors for this DSD (i.e., toxicity factors based on effects induced specifically and solely by TMBs) as accurately ascertaining the contribution of TMBs alone to the reported toxic effects would be problematic. TMB isomer studies (e.g., Korsak and Rydzynski 1996, Korsak et al. 1997, Korsak et al. 2000a,b) were available for this purpose and provide LOAELs and POD_{HEC} values for TMB-specific effects for derivation of the chronic ReV and ESL.

4.1.2.3 Developmental and Reproductive Studies

In addition to the information presented in Section 3.1.2.3 on the potential developmental and reproductive effects of TMBs, the continued discussion of McKee et al. (1990) below (most taken almost verbatim from NRC 2012) is relevant in the context of development of the chronic ReV and ESL. However, some of the discussion in Section 3.1.2.3 is worth reiterating here first.

While the TCEQ agrees with USEPA (2013) that individual TMB isomer studies are preferable for deriving toxicity factors specific to TMBs, relevant data (e.g., that address a potential data gap) should not be ignored because they are not ideal for this narrow purpose. While C9 aromatic hydrocarbon data are not amenable to deriving TMB-specific toxicity factors (e.g., conducting dose-response assessments of individual isomers), the consideration of several factors suggests that they are nevertheless relevant to the potential of TMBs to cause developmental/reproductive effects. First, in the study discussed below (McKee et al. 1990) TMBs comprised the majority of the C9 fraction to which animals were exposed. Second, exposure to the significant amount of TMBs present as part of the C9 fraction appears more representative of typical public exposure than individual TMBs as “vehicle emissions are expected to be the major anthropogenic source of TMBs” due to the widespread use of the C9 fraction as a component of gasoline (USEPA 2012). This consideration mitigates concern about some potential difference in toxicity between a TMB mixture study and individual TMB isomer study as routine public exposure may be expected to be to a TMB mixture as part of the C9 component in gasoline (note that this DSD applies the most conservative values to TMB

mixtures in addition to the individual isomers). Additionally, use of these data (at least in a limited way) may be viewed as consistent with USEPA (2000), which suggests using available mixture toxicity data for mixtures of concern. This consideration applies here to the extent that C9 fraction-associated vehicle emissions are expected to be the major anthropogenic source of exposure to TMBs, although this DSD does not derive toxicity factors specifically for this fraction but for TMBs which could be emitted (alone or as part of a mixture) from any source. However, the goal of deriving TMB-specific toxicity factors, in the absence of other more specific and arguably more relevant or complementary data, does not justify disregarding data relevant and informative as to the potential of TMBs to cause effects of potential concern (e.g., developmental/reproductive) despite that the data cannot be used directly to derive the specific toxicity factors desired. Lastly, USEPA (2013) acknowledges in Appendix E that the study included below (McKee et al. 1990) is exceptional among C9 fraction studies in that it clearly observed developmental and reproductive toxicity. Collectively, these considerations suggest that these C9 fraction data are largely relevant and informative here but that the toxicity factors in this DSD should be TMB specific. More specifically, without having to serve as surrogate data for any specific isomer, these C9 data enhance the database in regard to the types of developmental/reproductive effects that TMBs may cause and provide an indication of how the levels producing such effects compare to those of specific TMB isomers producing neurological effects.

In a well-conducted, three-generation reproductive study (McKee et al. 1990), F0 groups of 30 or 40 male and 30 or 40 female Charles River COBS CD rats were exposed to C9 aromatic hydrocarbons at target concentrations of 0, 100, 500, or 1,500 ppm for 6 h/day, 5 days/week for 10 weeks prior to mating and during the two-week mating period. Mean analytically-determined exposure concentrations based on hourly measurements during the study were 103, 495, and 1,480 ppm, respectively. The composition of the test material contained 55.1% TMBs (8.37% 1,3,5-TMB, 40.5% 1,2,4-TMB, 6.18% 1,2,3-TMB). The remainder of the mixture was comprised of o-xylene, cumene, n-propyl benzene, and 4-, 3-, and 2-ethyltoluene. Due to the presence and similarity (e.g., structural, metabolic, toxicological) of other C9 alkylbenzenes (e.g., ethyltoluenes, cumene), it cannot be assumed that the TMBs alone are responsible for the effects observed (rather it is the cumulative effect of exposure) and the total C9 exposure concentration is considered the most relevant dose metric (e.g., xylenes, cumene, and toluene can also cause neurotoxicity). After mating, the F0 males were sacrificed and necropsied. F0 females continued to be exposed for 6 h/day, 7 days/week on gestation days 0-20, and exposure was resumed on lactation days 5-21. Following weaning, females were sacrificed and necropsied. F1 rats were exposed for ten weeks beginning at 5-7 weeks of age and then mated to produce the F2 generation. Exposure of the F2 generation, used to produce the F3 generation, began immediately after the lactation period (i.e., on postnatal day 22).

All F0 and F1 parental males survived the exposure. In the 1,480 ppm groups, a total of seven of 30 F0 females, six of 30 F1 females, 36 of 40 F2 males, and 34 of 40 F2 females died or were sacrificed. Clinical signs of toxicity of ataxia (41 animals) and reduced motor activity (19) were

described in the F1 parental animals at 1,480 ppm. During premating, males and females of all generations exposed to 495 and 1,480 ppm and the F2 animals exposed to103 ppm had reduced body weight and body weight gain. The difference in toxicity for the F2 generation was presumably due to the lower age of the F2 generation at the beginning of exposure. Body weight gain decreased 5-7% in both F0 females and males at 495 ppm, and decreased 5-7% and 14-16%, respectively, at 1,480 ppm. During the exposure period for F1 animals, body weight gain was approximately 5-7% below control values in males in the 495 ppm group, 21-25% below in males from the 1,480 ppm group, and 9-14% below in females from the 1,480 ppm group. During the exposure period for F2 animals, at week 4 the male rats in the 1,480 ppm group had mean body weights 40% below controls, and remained 31-38% below for the remainder of the exposure period. Mean body weights of the females were 35% below controls and remained 21-30% below. In the 103 and 495 ppm exposure groups, weights of F2 males and females were initially below control values (i.e., males were 10% and 16% below in the 103 and 495 ppm groups, respectively, females were 6% and 16% below) and continued at approximately the same relative levels throughout the exposure period. Food consumption was similar between the treated and control groups throughout the study and gross necropsy of the adults was unremarkable.

The precoital interval was increased at 1,480 ppm for all generations. Mating, gestation, and fertility indices were not affected in the F0 or F2 generations, although only six F3 litters were produced due to deaths of the F2 animals at this high exposure level. At 1,480 ppm, F1 parental animals had decreased male fertility index, which did not occur in F0 or F2 males, and decreased live litter size at birth. F2 offspring in the 1,480 ppm group had a reduced litter size (8.7 vs 12.4 in controls) and live birth (i.e., gestational survival) index (85.1% vs 97.5% in controls). Body weight of F1, F2, and F3 pups exposed at 1,480 ppm was significantly less than that of controls beginning on lactation day 7, except for F2 pups on day 21. In addition, body weights of the F3 pups in the 1,480 ppm group were lower than that of controls at birth, and in the 495 ppm F3 group were lower starting on lactation day 14. While F1 pups had statistically decreased body weight on day 14 at 103 ppm, this reduction was not observed at any other time point (lactation day 0-21), the decreases across exposure groups on day 14 were non-monotonic, and F1 pup body weight was not significantly decreased at 495 ppm for any time point. The study authors conclude that there was little evidence of reproductive effects (although TCEQ notes evidence at 1,480 ppm), and that while prenatal exposure to levels producing some maternal toxicity resulted in delayed development (e.g., decreased fetal body weight), there were no developmental effects at levels which were not also maternally toxic (McKee et al. 1990).

The TCEQ considers the lowest LOAEL from this three-generation reproductive study to be the minimal LOAEL of 103 ppm for decreased body weight in F2 males (10% decrease) but not females (6%) exposed beginning early in life (i.e., immediately after the lactation period), although USEPA (2013) cites 103 ppm as the NOAEL. This minimal LOAEL is over 4-fold higher than the subchronic LOAEL (25 ppm) for 1,2,3-TMB-induced neurotoxicity (i.e., decreased pain sensitivity), which suggests that protecting against potential neurotoxicity as the

critical chronic adverse effect will also protect against potential developmental/reproductive effects.

4.1.3 MOA Analysis

Both short- and long-term studies demonstrate that inhalation exposure to TMB concentrations of sufficient magnitude and duration can result in CNS/neurological effects. Although little is known about the mechanism of TMB toxicity (NRC 2012), Section 3.1.3 contains a discussion of possible MOAs for TMB-induced neurological effects.

4.1.4 Key Study PODs, Dosimetric Adjustments, and Critical Effect

Based on the key study of Korsak and Rydzynski (1996) discussed above, USEPA (2013) conducted PBPK and/or BMD modeling to identify subchronic PODs for both TMB isomers tested. Then, USEPA calculated the corresponding POD_{HEC} values for the critical effects of 1,2,3- and 1,2,4-TMB-induced neurotoxicity (i.e., decreased pain sensitivity). The POD_{HEC} values for the two isomers were essentially identical (see below), and will be used by TCEQ to calculate the chronic ReV. The following was taken (much of it verbatim) from USEPA (2013).

4.1.4.1 Dosimetric Adjustments and POD for 1,2,4-TMB

For 1,2,4-TMB, the available rat PBPK model (Hissink et al. 2007) was used to convert non-continuous external concentrations (in mg/m^3) from the animal study (highest dose dropped) to the internal blood metric of weekly average venous 1,2,4-TMB concentration (in mg/L). It was assumed that the parent compound is the toxic moiety of interest and that average venous blood concentration of 1,2,4-TMB represents target tissue dose, and internal dose metrics may more closely correlate with toxic response than external concentrations (e.g., dosimetry can be nonlinear due to metabolic saturation). These internal blood metrics for the rat were then used as the dose inputs for BMD modeling. A benchmark response (BMR) equal to a 1 standard deviation (SD) change in the control mean for decreased pain sensitivity was used. A $BMDL_{1SD}$ of 0.086 mg/L (exponential model 4) was estimated for decreased pain sensitivity in male rats exposed subchronically to 1,2,4-TMB via inhalation. The available human PBPK model (Hissink et al. 2007) was then used to estimate the 1,2,4-TMB human equivalent concentration (HEC) of 15.8 mg/m^3 from the $BMDL_{1SD}$ of 0.086 mg/L assuming continuous exposure (24 h/day, 7 days/week). See USEPA (2013) for more detailed information.

Although the model simulates the data overall, the USEPA Chemical Assessment Advisory Committee (CAAC) that peer reviewed the PBPK model indicated that it provides poor fit to high rat 1,2,4-TMB exposures (USEPA 2014). Consequently, as an alternative to revising the rat PBPK model to provide better high-dose fit, the CAAC panel suggested first BMD modeling external rat dose (as opposed to internal dose from PBPK). This process was reported to alleviate the need for USEPA to revise the rat PBPK model and drop the high dose for BMD modeling. PBPK modeling can then be used for extrapolation of the BMD from rats to humans. The CAAC reported the POD_{HEC} for 1,2,4-TMB (15.8 mg/m^3) to be unchanged by this alternative process

(USEPA 2014), which primarily differs from that discussed above (and in USEPA 2013) in that BMD modeling is performed first (prior to any PBPK modeling).

4.1.4.2 POD and Dosimetric Adjustments for 1,2,3-TMB

For 1,2,3-TMB, a $BMDL_{1SD}$ of 97.19 mg/m^3 (linear model) was estimated for decreased pain sensitivity in male rats exposed via inhalation for 90 days (6 h/day, 5 days/week) in Korsak and Rydzynski (1996). Because no PBPK model exists for 1,2,3-TMB, USEPA (2013) calculated the duration-adjusted POD as follows, which is consistent with TCEQ (2015a):

POD_{ADJ} (mg/m^3) = POD (mg/m^3) × h exposed per day/24 h × days exposed per week/7 days = 97.19 mg/m^3× 6 h/24 h × 5 days/7 days = 17.36 mg/m^3

Thus, the duration-adjusted $BMDL_{1SD}$ for 1,2,3-TMB was calculated to be 17.36 mg/m^3.

As no PBPK model was available for 1,2,3-TMB, default dosimetry methodologies were used by USEPA (consistent with TCEQ 2015a) to estimate the POD_{HEC}, based on the ratio of the animal/human blood:air partition coefficients (as in Section 3.4 of this DSD):

$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 17.36$ mg/m^3 x 62.6/66.5 = 16.3 mg/m^3

4.1.4.3 Key Study POD and Critical Effect

The POD_{HEC} values of 15.8 and 16.3 mg/m^3 for 1,2,4- and 1,2,3-TMB, respectively, are remarkably similar considering the significantly different methodologies used to derive them (e.g., PBPK internal dose metric versus default duration and dosimetric adjustments for external concentration). The TCEQ adopts the mean POD_{HEC} of 16 mg/m^3 (3.3 ppm) for the critical effect of TMB-induced neurotoxicity (i.e., decreased pain sensitivity) based on the key study of Korsak and Rydzynski (1996) to derive the chronic ReV and ESL for TMBs (individual isomers and any mixture thereof).

4.1.5 Adjustments of the POD_{HEC} and Application of UFs

For the noncarcinogenic effects of TMBs, UFs are applied to a POD to derive the chronic ReV (i.e., assume a nonlinear MOA for a noncarcinogenic endpoint). The following UFs were considered appropriate for application to the POD_{HEC} of 16 mg/m^3: 10 for UF_H, 3 for extrapolation from animals to humans (UF_A), 3 for use of a subchronic study (UF_{Sub}), and 1 for UF_D; total UF = 90.

- An UF_H of 10 was considered appropriate to account for potential intrahuman variability since information on potentially sensitive subpopulations to long-term exposure is lacking (e.g., no information is currently available on variability in the expression of enzymes involved in TMB metabolism). TCEQ also notes that effects other than neurotoxicity (e.g., inflammatory lung lesions, effects on cells in bronchoalveolar lavage fluid, decreased red

blood cells, decreased clotting time, neutrophil effects) have similar subchronic POD_{HEC} values (USEPA 2013), although not the critical effect, and would require a full UF_H of 10.

- An UF_A of 3 was considered appropriate to account for potential interspecies toxicodynamic differences since dosimetric adjustment for toxicokinetic differences was conducted.

- A UF_{Sub} of 3 was considered appropriate to account for the use of a subchronic study because it appears that longer-term exposure could potentially produce a more pronounced neurotoxic effect (and lower POD). For example, the TCEQ notes that there were exposure duration-related increases in rotarod test failures for 1,2,3-TMB in the subchronic portion of Korsak and Rydzynski (1996). More specifically, at 1,230 mg/m^3 (250 ppm) 1,2,3-TMB the test failures consistently increased from approximately 40% at week 4 to about 70% at week 13. Likewise, at 492 mg/m^3 (100 ppm) 1,2,3-TMB the test failures consistently increased from approximately 10% at week 4 to about 40% at week 13. These results indicate some potential for greater neurotoxicity with even longer (i.e., chronic) exposure. On the other hand, while the duration-response curves for these concentrations (492 and 1,230 mg/m^3 1,2,3-TMB) in Figure 3 of the study had not plateaued by week 13, their slopes decrease (i.e., becoming less steep) between weeks 4 and 13, and the duration-response curve for the lower concentration (123 mg/m^3 or 25 ppm 1,2,3-TMB) most relevant to the POD indicates no increased response (i.e., has a plateau) between weeks 8 and 13. Additionally, there was no difference in rotarod performance (i.e., the duration-response curve plateaus) between weeks 8 and 13 for rats exposed to 1,230 mg/m^3 (250 ppm) and 492 mg/m^3 (100 ppm) 1,2,4-TMB (psuedocumene) and between weeks 4 and 13 for rats exposed to 123 mg/m^3 (25 ppm) 1,2,4-TMB. These latter results from the key study mitigate some concern for potential greater toxicity (e.g., severity) with chronic exposure. Accordingly, an UF_{Sub} of 3 was considered appropriate (USEPA 2013 cites other rational for selection of the same value of 3).

- An UF_D of 1 was considered applicable because of the strength of the TMB toxicity database. For example, there are three well-designed subchronic studies that assessed effects in multiple organ systems in Wistar rats exposed to 1,2,4-TMB via inhalation (Korsak and Rydzynski 1996, Korsak et al. 2000a, Korsak et al. 1997), two well-designed subchronic studies assessed effects in multiple organ systems in Wistar rats exposed to 1,2,3-TMB (Korsak and Rydzynski 1996, Korsak et al. 2000b), and a well-designed developmental toxicity (Saillenfait et al. 2005) of two other isomers (1,2,4- and 1,3,5-TMB) in Sprague-Dawley rats that observes developmental toxicity at exposure levels much higher than those eliciting neurotoxicity and other effects in adult animals (USEPA 2013). Additionally, a well-conducted developmental/reproductive study (McKee et al. 1990) evaluating developmental effects in mice (exposure on gestation days 6-15) and reproductive/developmental effects in rats (three-generation) exposed to a C9 aromatic hydrocarbon mixture containing over 55% TMBs (see Sections 3.1.2.3 and 4.1.3.3) also suggests that protecting against neurotoxicity will also protect against potential developmental/reproductive effects. Thus, the relevant database is considered medium-high.

The TCEQ notes that although relevant (see Section 4.1.3.3), all C9 fraction studies were excluded by USEPA (2013) because C9 is a mixture, isomer-specific studies generally provide lower LOAELs, and TMB-specific RfCs cannot be calculated based on mixture studies (regardless of the information they can provide). Consequently, USEPA proposes a UF_D of 3 due to the absence of TMB isomer-specific multigenerational reproductive and/or developmental studies. By contrast, for reasons cited in Section 4.1.2.3, the TCEQ considers the developmental and three-generation reproductive study results of McKee et al. (1990) as particularly informative. USEPA (2013) acknowledges in Appendix E that this study is exceptional among C9 fraction studies in that it clearly observed developmental and reproductive toxicity. Furthermore, this study's results appear consistent with those observed in the TMB isomer developmental study of Saillenfait et al. (2005). USEPA considers 495-500 ppm as the LOAEL (100 ppm as the NOAEL) for C9-induced developmental and reproductive effects in McKee et al. based on decreased fetal body weight (see Appendix E of USEPA 2013). Decreased fetal body weight occurred at a similar 1,3,5- and 1,2,4-TMB LOAEL (600 ppm) in the developmental study of Saillenfait et al. (also associated with decreased maternal body weight), although concentrations as low as 100 ppm were tested. Thus, there is no appreciable difference in the C9 and isomer-specific TMB concentrations which induced decreased fetal body weight in these two studies (in fact, the C9 LOAEL is lower). Additionally, while no clinical signs of toxicity were observed at a 1,2,4-TMB concentration up to 900 ppm or a 1,3,5,-TMB concentration up to 1,200 ppm in Saillenfait et al., multiple clinical signs of toxicity were observed at 1,480-1,514 ppm C9 in McKee et al., including neurological effects (e.g., weakness, circling, ataxia, reduced motor activity). Thus, the TMB isomer study did not show clinical signs of toxicity or neurotoxicity at a lower concentration than the C9 study (or at any concentration for that matter). Lastly, while no skeletal or other malformations were observed with either TMB isomer at concentrations up to 1,200 ppm, the C9 fraction induced a number of effects (i.e., cleft palate, reduced ossification, post-implantation loss with reduced live fetuses/dam) at 1,514 ppm (equating to 834 ppm TMBs based on the TMB content of the C9), including high incidences of cleft palate and reduced ossification of the skull. The TMB isomer study did not show these developmental effects at lower concentrations or any concentration (even those inducing decreased maternal body weight), while the C9 study did and with high incidences (at just a 26% higher C9 concentration than the 1,200 ppm used for 1,3,5-TMB in Saillenfait et al.). Along with the considerations discussed in Section 4.1.2.3, the consistency of the results from McKee et al. (1990) and Saillenfait et al. (2005) for endpoints of concern support inclusion of the McKee et al. study in the database and selection of an appropriate UF_D value.

Finally, the TCEQ notes that for a developmental effect from a study absent from the database USEPA is considering to become the critical effect in the USEPA (2013) analysis (critical POD values of 84 and 97 mg/m^3), the new POD would have to be more than 58 times lower than the 100 ppm (492 mg/m^3) NOAEL identified by USEPA for developmental effects in McKee et al. (1990) or even the 100 ppm (492 mg/m^3) NOAEL for decreased fetal

weight secondary to decreased maternal body weight based on the TMB isomer study of Saillenfait et al. (e.g., 492 mg/m^3 / USEPA POD of 84 mg/m^3 x 10 for pulling out the UF_D and UF_{Sub} values of 3 each since the database would be completed by the new study and UF_{Sub} would not be applicable = 58; 492 mg/m^3 / 58 = 8.5 mg/m^3; POD of 8.5 mg/m^3 x 6 h/24 h x 5 d/7 d / total applicable UF of 30 (UF_A 3, UF_H 10, UF_D 1, UF_{Sub} n/a) = proposed RfC of 5E-02 mg/m^3). Based on the appreciable information and considerations discussed herein, this appears improbable.

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

The UFs discussed above were applied to the POD_{HEC} (16 mg/m^3) to derive the chronic ReV:

chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)
= 16 mg/m^3 / (10 x 3 x 3 x 1)
= 16 mg/m^3 / 90
= 0.177 mg/m^3
= 180 µg/m^3 or 37 ppb (rounded to two significant digits)

In deriving the chronic ReV, no numbers were rounded between equations until the ReV was calculated. The chronic ReV was rounded to two significant figures, resulting in a value of 180 µg/m^3 (37 ppb), and then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 54 µg/m^3 (11 ppb) (Table 5).

Table 5. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	**Values and Descriptions**
Study	Korsak and Rydzynski (1996)
Study Population	10 male Wistar rats per exposure group
Study Quality	Medium
Exposure Concentrations	0, 123, 492, or 1,230 mg/m^3 1,2,3- or 1,2,4-TMB
Exposure Duration	6 h/day, 5 days/week for 90 days
Critical Effects	Neurotoxicity (e.g., decreased pain sensitivity) in rats
PODs ($BMDL_{1SD}$)	0.086 mg/L blood for 1,2,4-TMB using PBPK/BMD 97.19 mg/m^3 for 1,2,3-TMB using BMD
Extrapolation to continuous exposure (POD_{ADJ})	15.8 mg/m^3 for 1,2,4-TMB using PBPK 17.36 mg/m^3 for 1,2,3-TMB using default procedure (TCEQ 2015a)
POD_{HEC}	16 mg/m^3 (3.3 ppm), the mean of: 15.8 mg/m^3 for 1,2,4-TMB 16.3 mg/m^3 for 1,2,3-TMB
Total UF	90
Interspecies UF	3
Intraspecies UF	10
Subchronic to Chronic UF	3
Incomplete Database UF *Database Quality*	1 Medium-high
Chronic ReV (HQ = 1)	**0.180 mg/m^3 or 180 µg/m^3 (37 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.054 mg/m^3 or 54 µg/m^3 (11 ppb)**

4.2 Carcinogenic Potential

USEPA (2013) provides the following (most taken verbatim) on the carcinogenic weight of evidence (WOE) for TMBs:

The database for the TMBs provides "inadequate information to assess carcinogenic potential" of these isomers. This characterization is based on the fact that there is no information regarding the carcinogenicity of TMBs in humans and that the only animal study available on carcinogenicity observed no statistically significant carcinogenic effects. In the animal carcinogenicity study identified (Maltoni et al. 1997), involving exposure to 1,2,4-TMB by oral gavage, an increased incidence of total malignant tumors in both sexes and head cancers (predominantly neuroethesioepithelioma) in males was observed in exposed rats, but no statistical analyses were reported. When USEPA independently performed the Fisher's exact test on the reported data, no statistically significant effects were observed. No studies regarding the carcinogenicity of 1,2,3- or 1,3,5-TMB were identified in the available scientific literature.

Additionally, in the only study investigating the genotoxicity of TMB isomers discussed in USEPA (2013), Janik- Spiechowicz et al. (1998) observed negative results in *in vitro* genotoxicity assays (i.e., Ames mutation assay in Salmonella) involving 1,2,4- and 1,3,5-TMB. However, 1,2,3-TMB was observed to induce gene mutations in all *Salmonella typhimurium* strains tested. All three isomers failed to induce micronuclei in mouse bone marrow cells. Janik-Spiechowicz et al. observed an increased incidence of sister chromatid exchange (SCE) in mice exposed to all three TMB isomers (individually); however, this observation does not provide a specific indication of mutagenic potential. Given the findings regarding the *in vitro* genotoxicity of the TMB isomers, and increased frequency SCEs does not provide specific indication of mutagenic potential, the evidence from this study is inadequate to conclude that any TMB isomer is genotoxic. While Kim et al. (2006) is not included in USEPA (2013), that study investigated the genotoxicity of 1,2,4-TMB using the Ames reverse mutation test at doses of 100, 50, 25, 12.5, 6.25 µg/plate, which did not induce mutagenicity in *Salmonella typhimurium* TA98, TA100, TA1535, TA 1537 or *Escherichia coli* WP2uvrA, with or without metabolic activation. The authors reported that 1,2,4-TMB has no mutagenic potential under the conditions of their study.

The TCEQ concurs with the USEPA (2013) carcinogenic WOE classification for TMBs, which is "*Data Are Inadequate for an Assessment of Human Carcinogenic Potential*." Consequently, a chronic carcinogenic inhalation value will not (in fact cannot) be developed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 180 µg/m^3 (37 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 54 µg/m^3 (11 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 54 µg/m^3 (11 ppb) (Table 2). The chronic ReV of 180 µg/m^3 (37 ppb) will be used for the evaluation of ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5 Subchronic Inhalation Observed Adverse Effect Level

Observed inhalation adverse effect levels are described in more detail in Section 3.4. Regarding critical effects due to subchronic TMB exposure, a BMD_{1SD} of 152 mg/m^3 for decreased pain sensitivity due to 1,2,3-TMB exposure in the subchronic Korsak and Rydzynski (1996) rat study is provided in USEPA (2013) (see Table C-9). This value is similar to the study LOAEL of 123 mg/m^3 for 1,2,3-TMB-induced decreased pain sensitivity (i.e., neurotoxicity), which was used as the animal subchronic inhalation observed adverse effect level for extrapolation to humans. No duration adjustment was made (TCEQ 2015a).

In the subchronic exposure portion of Korsak and Rydzynski (1996), 1,2,3-TMB acted as a Category 3 vapor, producing a systemic effect as the critical adverse effect (i.e., neurotoxicity). The default pharmacokinetic animal-to-human dosimetric adjustment for a Category 3 vapor is multiplication of the animal-based POD by the ratio of the animal/human blood:gas partition coefficients (TCEQ 2015a):

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

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

Blood:air partition coefficients for 1,2,3-TMB have been reported for humans and rats in Meulenberg and Vijverberg (2000). The reported partition coefficients of 66.5 (human) and 62.6 (rat) for 1,2,3-TMB are used in calculation of the POD_{HEC}:

$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H)$ = 123 mg/m^3 x 62.6/66.5 = 116 mg/m^3 (24 ppm)

Thus, following animal-to-human dosimetric adjustment, the subchronic inhalation observed adverse effect level based on this study is estimated to be 116 mg/m^3 (24 ppm). This concentration, 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 study (90 days for 6 h/day, 5 days/week) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The

subchronic inhalation observed adverse effect level of 116 mg/m^3 (24 ppm) is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the subchronic inhalation observed adverse effect level of 116 mg/m^3 (24 ppm) and the chronic ReV of 0.180 mg/m^3 is a factor of 644.

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