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Methyl Ethyl Ketone

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

LIST OF TABLES	II
LIST OF 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 RE _V 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	4
3.1.2.1.1 Key Human Study (Dick et al. 1992).....	5
3.1.2.1.2 Other Human Studies	6
3.1.2.2 Animal Studies.....	8
3.1.2.2.1 Key Animal Study (Schwetz et al. 1991).....	8
3.1.2.2.2 Supporting Animal Studies	9
3.1.3 Mode-of-Action (MOA) Analysis and Dose Metric	11
3.1.4 Point of Departure (POD) for Key Human and Animal Study	11
3.1.4.1 Key Human Study	11
3.1.4.2 Supporting Animal Study	11
3.1.5 Dosimetric Adjustments	12
3.1.5.1 Default Exposure Duration Adjustments	12
3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure	12
3.1.6 Adjustments of the <i>POD</i> _{HEC}	13
3.1.6.1 Neurological Effects and Sensory Irritation in Humans (Dick et al. 1992).....	13
3.1.6.2 Developmental Effects in Mice (Schwetz et al. 1991)	13
3.1.7 Critical Effect.....	14
3.1.8 Health-Based Acute Re _V and ^{acute} ESL.....	14
3.2. WELFARE-BASED ACUTE ESLs	14
3.2.1 Odor Perception.....	14
3.2.2 Vegetative Effects.....	15
3.3. SHORT-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION	15
CHAPTER 4 CHRONIC EVALUATION.....	16
4.1 NONCARCINOGENIC POTENTIAL.....	16
4.1.1 Physical/Chemical Properties and Key Study	16
4.1.1.1 Physical/Chemical Properties	16
4.1.1.2 Human Studies	16
4.1.1.3 Animal Studies.....	17

4.1.2 Mode of Action and Dose Metric	18
4.1.3 PODs for Key Study and Dosimetric Adjustments.....	19
4.1.3.1 Default Exposure Duration Adjustments	19
4.1.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure	19
4.1.4 Adjustments of the POD_{HEC}	19
4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$	20
4.1.6 Comparison of TCEQ's Chronic ReV to USEPA's Chronic Reference Concentration	21
4.2 CARCINOGENIC POTENTIAL.....	22
4.3 WELFARE-BASED CHRONIC ESL	22
4.4 LONG-TERM ESL AND VALUES FOR AIR MONITORING EVALUATION.....	22
CHAPTER 5 REFERENCES	22
5.1 REFERENCES CITED IN THE DEVELOPMENT SUPPORT DOCUMENT	22
5.2 OTHER STUDIES AND DOCUMENTS REVIEWED BY THE TD	26
APPENDIX A BENCHMARK DOSE MODELING.....	28

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. Summary of Acute Human Studies	7
Table 5. Summary of Acute Animal Inhalation and Developmental Studies.....	10
Table 6. Derivation of the Acute ReV and $^{acute}ESL$	14
Table 7. Accepted Odor Studies Conducted for MEK	15
Table 8. Derivation of the Chronic ReV and $^{chronic}ESL$	21
Table A-1. Mean Fetal Body Weight (mice) and Standard Deviation ^a	28
(Mast et al. 1989 and Schwetz et al. 1991).....	28
Table A-2. Benchmark Dose Modeling Results Fetal Body Weight.....	28
Table A-3. Misaligned Sternebrae (mice) ^a (Mast et al. 1989 and Schwetz et al. 1991)	29
Table A-4. Benchmark Dose Modeling Results Misaligned Sternebrae	29

List of Acronyms and Abbreviations

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A	animals
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
AMCV	Air Monitoring Comparison Value
BMC	benchmark concentration
BMCL	benchmark concentration 95% lower confidence limit
BMDS	Benchmark Dose Software
⁰ C	degrees centigrade
CES05	critical effect size corresponding to a 5% relative decrease in the mean when compared to controls
CES	critical effect size
CNS	central nervous system
DSD	development support document
ET	extrathoracic
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 _{linear(c)}	chronic health-based Effects Screening Level for linear dose response cancer effect
^{chronic} ESL _{linear(nc)}	chronic health-based Effects Screening Level for linear dose response noncancer effects
^{chronic} ESL _{nonlinear(c)}	chronic health-based Effects Screening Level for nonlinear dose response cancer effects
^{chronic} ESL _{nonlinear(nc)}	chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
^{chronic} ESL _{veg}	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week
GD	gestation day
h	hour
H	humans
H _{b/g}	blood:gas partition coefficient
(H _{b/g}) _A	blood:gas partition coefficient, animal

List of Acronyms and Abbreviations

$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
μg	microgram
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
min	minute
MEK	methyl ethyl ketone
MOA	mode of action
n	number
N/A	Not applicable
NAC	National Advisory Committee
n-BA	n-butyl acetate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
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
ReV	reference value
RGDR	regional gas dose ratio
SA	surface area
SAR	structure-activity relationship
SCOB	scheduled-controlled operant behavior
SD	Sprague-Dawley
SMCs	self-reported multiple chemical sensitivity
SPGT	serum glutamic-pyruvic transaminase
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor

List of Acronyms and Abbreviations

UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
V_E	minute volume

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 methyl ethyl ketone (MEK). Please refer to the Air Monitoring Comparison Value Document (AMCV Document) available at <http://www.tceq.state.tx.us/implementation/tox/AirToxics.html> for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on MEK's physical/chemical properties.

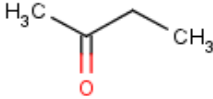
Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air		
Short-Term Values	Concentration	Notes
Acute ReV	59,000 $\mu\text{g}/\text{m}^3$ (20,000 ppb) Short-Term Health	Critical Effect(s): Neurological effects; sensory irritation in human volunteers
$^{\text{acute}}\text{ESL}_{\text{odor}}$	1,300 $\mu\text{g}/\text{m}^3$ (440 ppb) Odor	50% detection threshold
$^{\text{acute}}\text{ESL}_{\text{veg}}$	- - - Short-Term Vegetation	Insufficient data
Long-Term Values	Concentration	Notes
Chronic ReV	8,800 $\mu\text{g}/\text{m}^3$ (3,000 ppb) Long-Term Health	Critical Effect(s): Freestanding NOAEL in Fischer 344 rats
$^{\text{chronic}}\text{ESL}_{\text{linear}(c)}$ $^{\text{chronic}}\text{ESL}_{\text{nonlinear}(c)}$	- - -	Insufficient data
$^{\text{chronic}}\text{ESL}_{\text{veg}}$	- - - Long-Term Vegetation	No data found

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

Table 2. Air Permitting Effects Screening Levels (ESLs)		
Short-Term Values	Concentration	Notes
^{acute} ESL [1 h] (HQ = 0.3)	18,000 $\mu\text{g}/\text{m}^3$ (6,000 ppb) ^a	Critical Effect: Neurological effects; sensory irritation in human volunteers
^{acute} ESL _{odor}	1,300 $\mu\text{g}/\text{m}^3$ (440 ppb) Short-Term ESL for Air Permit Reviews	50% detection threshold
^{acute} ESL _{veg}	---	Insufficient data
Long-Term Values	Concentration	
^{chronic} ESL _{nonlinear(nc)} (HQ = 0.3)	2,600 $\mu\text{g}/\text{m}^3$ (900 ppb) ^b Long-Term ESL for Air Permit Reviews	Critical Effect: Freestanding NOAEL in Fischer 344 rats
^{chronic} ESL _{linear(c)} ^{chronic} ESL _{nonlinear(c)}	---	Insufficient data
^{chronic} ESL _{veg}	---	No data found

^a Based on the acute ReV of 59,000 $\mu\text{g}/\text{m}^3$ (20,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

^b Based on the chronic ReV of 8,800 $\mu\text{g}/\text{m}^3$ (3,000 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data		
Parameter	Value	Reference
Molecular Formula	C ₄ H ₈ O	ACGIH 2001
Chemical Structure		ChemID Plus 2009
Molecular Weight	72.10	ACGIH 2001
Physical State at 25°C	Liquid	TRRP 2006
Color	Colorless	ACGIH 2001
Odor	acetone-like, sweet and sharp with the hedonic tone described as neutral to unpleasant	ACGIH 2001; Leonardos et al. 1969; Hellman and Small 1974
CAS Registry Number	78-93-3	ACGIH 2001
Synonyms	2-Butanone MEK Ethyl methyl ketone Methyl acetone	ChemID Plus 2009
Solubility in water	223 g/L	ChemID Plus 2009
Log K _{ow}	0.26	TRRP 2006
Vapor Pressure	77.5 mm Hg at 20°C	ACGIH 2001
Relative Vapor Density (air = 1)	2.41	IPCS 1993
Melting Point	-86°C	ACGIH 2001
Boiling Point	79.6°C	ACGIH 2001
Conversion Factors	1 µg/m ³ = 0.34 ppb 1 ppb = 2.94 µg/m ³ at 25°C	ACGIH 2001

Chapter 2 Major Sources and Uses

MEK is used as a solvent in the surface coating industry, in the dewaxing of lubricating oils, and in the manufacture of colorless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues. MEK is seldom used alone in industrial applications; it is usually found in mixtures with acetone, ethyl acetate, n-hexane, toluene, or alcohols. It can be released into the air via the exhaust from cars and trucks, waste from manufacturing plants, and from natural sources such as from forest trees. It is also released into the air during its production, transport, storage, or use in commercial products (ATSDR 1992).

Chapter 3 Acute Evaluation

Acute inhalation exposure to high concentrations of MEK in humans has been reported to produce irritation of the eyes, nose, and throat. Central nervous system (CNS) depression, headache, and nausea have also been reported following acute inhalation exposure to humans. Additionally, at high concentrations MEK has been found to irritate respiratory tissues of animals. Acute inhalation investigations in rats indicate low toxicity from MEK exposure.

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

This section is based on a review of current literature as well as background readings in AEGL (2009) which describe in detail the acute toxicity of MEK. The Toxicology Division (TD) will use key studies from AEGL (2009) as well as data from the most recent publications, if available, to derive acute toxicity factors for MEK. The Development Support Document (DSD) is a summary of the key and supporting studies used by the TD to derive toxicity values.

3.1.1 Physical/Chemical Properties

MEK is a flammable, colorless liquid with an acetone-like odor or sweet and sharp odor with the hedonic tone described as neutral to unpleasant (Leonardos et al. 1969; Hellman and Small 1974). MEK is very soluble in water and all common industrial organic solvents. Other physical/chemical properties of MEK can be found in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

The following summary was obtained from AEGL (2009). See AEGL (2009) for the cited references:

“MEK is not a respiratory irritant at concentrations less than several thousand ppm. The clinical studies of Dick et al. (1984; 1988; 1992), Muttray et al. (2002), Seeber et al. (2002), and Shibata et al. (2002) did not report sensory irritation or neurobehavioral deficits at a constant concentration of 200 ppm for 2 or 4 hours or at concentrations that ranged between 10 and 380 ppm (average 188 ppm) over

4 hours. Twenty-four subjects exposed to 200 ppm for 4 hours found the concentration unobjectionable (Dick et al. 1992). In a series of neurobehavioral studies, a 4-hour exposure of human subjects to 200 ppm had no significant effect on a variety of behavioral tests (Dick et al. 1984; 1988; 1989). No irritation or subjective symptoms of sensory irritation were reported in four male subjects inhaling 200 ppm for 2 hours (Shibata et al. 2002). The same absence of sensory irritation and neurobehavioral deficits was reported by 19 male subjects inhaling 200 ppm for 4 hours (Muttray et al. 2002). During variable concentrations ranging from 10 ppm to 8-minute peaks at 380 ppm, five times over 4 hours, subjects rated annoyance and irritation either “hardly at all,” or “not at all” (Seeber et al. 2002). Both healthy subjects and subjects with sMCS were tested by Seeber et al. (2002). The primary subjective comment in these studies was a noticeable odor. In the study of Nelson et al. (1943) ten male and female volunteers exposed to MEK for 3-5 minutes judged 200 ppm as acceptable for an 8-hour exposure and 350 ppm as objectionable for an 8-hour exposure. There were no analytical measurements in this early study. Sensory irritation was reported in the Nakaaki (1974) study, but this study used variable concentrations and neurobehavioral results were difficult to interpret. Additional metabolism studies were conducted at concentrations of 25 to 400 ppm for 4 hours, but these studies did not address sensory irritation or neurotoxic effects. Although sensory irritation was not specifically addressed in the metabolism studies of Liira et al (1988a; 1988b; 1990a; 1990b) and Tada et al. (1972), volunteers were routinely exposed to concentrations of 200-400 ppm for 2-4 hours without apparent adverse effects.”

3.1.2.1.1 Key Human Study (Dick et al. 1992)

In a series of National Institute for Occupational Safety and Health (NIOSH)-sponsored studies involving acute, 4-hour (h) exposures of volunteers to 200 ppm MEK, no exposure-related changes in performance of psychomotor and mood tests or incidences of irritation were found (Dick et al. 1984; 1988; 1989; 1992). In the studies conducted in 1984, 1988, and 1989, no differences were observed between exposed and control groups on neurobehavioral tests including psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), postural sway, and a profile of mood states. Effects of exposure on mucous membrane irritation or symptoms such as headache or nausea were not examined. In the later study, chosen as the key study, subjects were exposed to 200 ppm MEK for 5 minutes followed by 4 h air or 200 ppm MEK for a total of 4 h (Dick et al. 1992). Neurobehavioral tests were performed at 2 and 4 h of exposure and 90 minutes post-exposure. No consistent, statistically significant, neurobehavioral effects were observed. Subjective questionnaires (self-administered paper and pencil tests) were administered to the participants who were to answer “yes” or “no” to questions regarding: (1) presence of odor; (2) strong odor; (3) objectionable odor; (4) headache (5) nausea; (6) throat dryness or coughing; (7) tearing, and (8) unpleasant exposure. Data on sensory and irritant effects showed a significant increase only in perception of strong odor. A 4-h free-standing NOAEL of 200 ppm (based primarily on neurological effects, and also based on the

absence of questionnaire effects such as sensory irritation) was selected from this study (Dick et al. 1992).

3.1.2.1.2 Other Human Studies

There were other more recent studies in humans (Table 4) which indicated a 200 ppm NOAEL for irritation (Muttray et al. 2002; Shibata et al. 2002). The Shibata et al. (2002) study was not chosen as the key study due to methodological discrepancies: males were exposed to MEK in combination with n-hexane. The Muttray et al. (2002) study investigated the effects of exposure to 200 ppm on the nasal mucosa of healthy males; the lack of irritation of the nasal mucosa supports the use of a 200 ppm NOAEL as determined by Dick et al. (1992). Nelson et al. (1943) may suggest 200 ppm as a LOAEL; however, exposure conditions were unclear. Although the Dick et al. (1992) study was designed to measure neurological effects, and was not intended to address irritation thresholds, it did utilize a larger study group that consisted of both males and females, and reported irritant effects were evaluated.

Table 4. Summary of Acute Human Studies

Concentration (ppm)	Exposure Duration	Effect/Type of Study	Reference
90-270 (average 150)	4 hours	Concentrations not held constant; underestimation of times of 5 to 30 seconds by men and expansion of variation of time estimation in women; questionable results	Nakaaki 1974
100 200 350	3-5 minutes 3-5 minutes 3-5 minutes	Slight nose and throat irritation Mild eye irritation in some subjects; judged satisfactory for 8-hour exposure Judged objectionable for 8-hour exposure	Nelson et al. 1943
100, 200	2 hours	Metabolism study; exposures in combination with n-hexane; constant workload of 50 watts; odor noticeable; no irritation, no subjective symptoms	Shibata et al. 2002
200	4 hours	No significance difference in choice reaction time, visual-vigilance, or pattern recognition tests	Dick et al. 1984
200	4 hours	No significant difference in psychomotor tests of choice reaction time, visual vigilance, dual task of auditory tone discrimination and tracking, memory scanning; postural sway; profile of moods states	Dick et al. 1988; 1989
200	4 hours	Noticeable strong, unobjectionable odor; subjective symptoms similar to control responses	Dick et al. 1992
200	4 hours	No irritation, no subjective symptoms; strong odor; increase in mucociliary transport time; nonsignificant changes in proinflammatory cytokines	Muttray et al. 2002
10 10-380 (five 8-minute peaks to 380 ppm; TWA app. 188)	4 hours 4 hours	No effect Intense odor; irritation rated "hardly at all;" subjects with self-reported multiple chemical sensitivity included in the study	Seeber et al. 2002; van Thriel et al. 2003b
25, 200, 400	4 hours	Metabolism studies; exercise incorporated into some protocols	Liira et al. 1988a; 1988b; 1990a; 1990b
300	2-4 hours	Metabolism study; sensory and neurobehavioral effects not addressed	Tada et al. 1972
300-600	Occupational	Central nervous system effects, possibly attributable to concurrent dermal exposure	Smith and Mayers 1944
33,000, 100,000 10,000 3300	Few breaths Few breaths Not given	Intolerable, irritation to eyes and nose Almost intolerable, irritation to eyes and nose Strong odor, moderately irritating to eyes and nose	Patty et al. 1935

Table 4 source: AEGL (2009). See AEGL (2009) for the cited references.

3.1.2.2 Animal Studies

Table 5 provides a summary of acute MEK inhalation animal studies. Results from studies of pregnant rodents exposed by inhalation to MEK indicate that developmental effects are the most sensitive, toxicologically relevant endpoint for laboratory animal inhalation exposure to MEK (USEPA 2003). Because short-term exposure during a critical period during gestation could result in adverse developmental effects, developmental studies are considered as part of the acute evaluation.

Inhalation exposure of experimental animals to approximately 3,000 ppm MEK (7 h/day) during gestation days 6-15 resulted in developmental toxicity in the presence of mild maternal toxicity in rats (Deacon et al. 1981) and mice (Schwetz et al. 1991), but in the absence of maternal toxicity in rats (Schwetz et al. 1974). These three developmental studies each determined a NOAEL of 1,000 ppm and a LOAEL of 3,000 ppm for maternal and fetal toxicity in rats and mice. Maternal toxicity included decreased weight gain in rats, and increased relative liver and kidney weights in mice. Fetal toxicity included increased incidences of gross and skeletal anomalies and delayed sternebral ossification in rats, and decreased fetal weight in mice. Exposure to 3,000 ppm MEK produced no overt neurological effects in the dams in any of these studies. No adverse effects were observed in pregnant rats exposed to 1,126 or 2,618 ppm MEK 7 h/day on days 6-15 of gestation (Schwetz et al. 1974).

Schwetz et al. (1991) was chosen as the key study because it was a well-conducted study and included a control group with three exposure groups with a significant dose-response relationship. The following sections discuss findings from these three developmental studies in detail.

3.1.2.2.1 Key Animal Study (Schwetz et al. 1991)

Groups of 10 virgin female Swiss CD1 mice and 33 plug-positive (day 0) females per exposure group were exposed by inhalation on gestation days (GD) 6-15 to mean concentrations of 0, 400, 1,000 and 3,000 ppm (nominal) [0, 398±9, 1,010±28, and 3,020±79 ppm (analytical)] (Schwetz et al. 1991 also reported as Mast et al. 1989 and NTP 1990). There was no evidence of overt maternal toxicity, although there was a slight, treatment-related increase in liver/body weight ratios that was significant at the highest concentration level. Mild fetal toxicity was apparent at 3,000 ppm as a reduction in mean fetal body weight, statistically significant for males. There was no increase in the incidence of intrauterine death, but there was an increased dose-related incidence of misaligned sternebrae, statistically significant at the highest concentration. There was no statistically significant increase in the incidence of any single malformation; however, several malformations which were not observed in the concurrent control group or the controls of contemporary studies were present at a low incidence - cleft palate, fused ribs, missing vertebrae, and syndactyly. The NOAEL was 1,010 ppm and the LOAEL was 3,020 ppm.

3.1.2.2.2 Supporting Animal Studies

Schwetz et al. (1974) exposed groups of 21-23 pregnant Sprague-Dawley (SD) rats in whole body dynamic exposure chambers to 1,126 or 2,618 ppm (analytical) MEK vapor, respectively, for 7 h/day on GD 6-15. The following endpoints were used to assess exposure-related effects: maternal body weight, food intake, liver weight, serum glutamic-pyruvic transaminase (SGPT) activity levels, number of implantations, litter size, fetal anomalies, incidence of resorptions, and fetal body measurements. No evidence of maternal toxicity or change in the number of resorptions was reported at any concentration. Statistically significant decreases in fetal weight and crown-rump length were observed at 1,126 ppm, but not at 2,618 ppm. The NOAEL was 1,126 ppm and the LOAEL was 2,618 ppm.

Deacon et al. (1981) attempted to replicate and improve upon the Schwetz et al. (1974) study. Deacon et al. (1981) exposed groups of 26, 19, 19, and 18 SD dams to nominal MEK concentrations of 0, 400, 1,000, or 3,000 ppm, respectively (7 h/day on GD 6-15). Average measured MEK concentrations were 412, 1,002, and 3,005 ppm. Dams exposed to 3,005 ppm MEK exhibited maternal toxicity that was demonstrated by a slight decrease in weight gain (326 g for 3,005 ppm group versus 351 g for control; $p < 0.05$ at gestation day 16).

Table 5. Summary of Acute Animal Inhalation and Developmental Studies				
Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Mouse	10,000 5,600 3,000 1,000 300	9.5 min 9.5 min 9.5 min 9.5 min 9.5 min	Mice unresponsive No response in most mice Response decreased by 75% Response slightly decreased No effect on response	Glowa 1987
Mouse	31,426 26,000 10,000	30 min 30 min 30 min	Calculated 50% decreased respiration Decrease in body movements Not anesthetic	Hansen et al. 1992
Mouse	5,000 9,000	10 min 10 min	15% decrease in respiratory rate 50% decrease in respiratory rate (RD ₅₀)	Stone et al. 1981
Developmental Studies				
pregnant SD Rat	1,126, and 2,618 (average measured concentrations)	7 h/day for 10 days (GD 6-15)	At 2,618 ppm minor effects on dams, decreased food consumption and weight gain, and increased water consumption; no effects on dams at 1,126 ppm LOAEL 2,618 NOAEL 1,126	Schwetz et al. 1974
SD dams	0, 412, 1,002, and 3,005 (average measured concentrations)	7 h/day on GD 6-15	Slight decrease in weight gain LOAEL 3,005 NOAEL 1,002	Deacon et al. 1981
Swiss (CD-1) mice	0, 398, 1,010, and 3,020 (analytical)	7 h/day, 7 day/wk (GD 6-15)	Significant signs of toxicity at the 3,020 ppm exposure level in offspring. Decreased body weight in male fetuses and both sexes combined (based on litter means), increased maternal liver-to-body weight ratio LOAEL 3,020 NOAEL 1,010	Schwetz et al. 1991; Mast et al. 1989

None of the exposure levels produced statistically significant effects in the incidence of pregnancy or resorption, the average number of implantations or live fetuses per dam, or fetal weight and length. No statistically significant differences in the incidences of external or soft-tissue alterations were observed in the exposed groups when compared with the control. A statistically significant difference in the incidence of litters with extra ribs was observed in the 3,005 ppm exposure group when compared with the controls. The incidence of extra ribs was 2/26 for control litters versus 0/19, 0/19, and 6/18 for 412, 1,002, and 3,005 ppm litters, respectively. Maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) was found at 3,005 ppm (LOAEL), but not at 412 or 1,002 ppm (NOAEL).

3.1.3 Mode-of-Action (MOA) Analysis and Dose Metric

The main effects produced in humans after exposure to high concentrations of MEK are irritation to the eyes and nose. Due to MEK's high water solubility, low concentrations may effectively be scrubbed by the nasal passages (AEGLE 2009). The mode of action (MOA) by which MEK induces irritation or developmental toxicity has not been clearly established. Therefore, a threshold or nonlinear dose-response assessment is assumed. Since the MOA of the toxic response is not fully understood, the exposure concentration of the parent chemical was used as the default dose metric.

3.1.4 Point of Departure (POD) for Key Human and Animal Study

3.1.4.1 Key Human Study

A freestanding NOAEL based on neurological effects and sensory irritation in humans (Dick et al. 1992) with a POD_{HEC} equal to the NOAEL of 200 ppm was selected for the key human study.

3.1.4.2 Supporting Animal Study

Data for the developmental effects described in the animal supporting study (Schwetz et al. 1991; Mast et al. 1989) were analyzed using benchmark dose modeling (see Appendix A). Models for continuous data (linear, polynomial, restricted power, and unrestricted power) in EPA's Benchmark Dose Software (BMDS version 2.0) were used to model mean fetal mouse body weight data (Mast et al. 1989), or mean percentage of misaligned sternbrae per litter (Schwetz et al. 1991). The complete data set can be found in Mast et al. (1989).

Changes in mean fetal body weight were analyzed using the average fetal weight for each litter. For a decrease in mean fetal body weight, a critical effect size (CES) was defined in terms of a prespecified level of response, corresponding to a 5% relative decrease in the mean when compared to controls (CES_{05}) (Kavlock et al. 1995; Allen et al. 1996). For abnormal sternbrae, a 5% relative decrease in the mean when compared to controls (CES_{05}) was used based on the findings by Allen et al. (Allen et al. 1994) that indicated the CES_{05} for malformed fetuses was similar to study NOAELs. The CES results for one standard deviation (SD) (CES_{1SD}) were also calculated and are presented in Appendix A for comparison purposes as suggested by USEPA (2000).

All models adequately modeled the experimental mean fetal body weight data with 95% confidence (i.e., goodness of fit p-value and scaled residual values did not imply rejection at the 5% significance level) and visual inspection of the dose-response curve indicated an adequate fit (Appendix A). However, the linear model had the lowest Akaike's Information Criterion (AIC) with a benchmark concentration level at the CE_{05} (BMC_{05}) of 3,248 ppm and 95% confidence limit on the BMC_{05} ($BMCL_{05}$) of 2,246 ppm.

The sternebrae data were not amenable to modeling. The only model that adequately modeled the experimental misaligned sternebrae data with 95% confidence was the polynomial model, but the dose-response curve was nonmonotonic (Appendix A). According to guidance in USEPA (2000), if the data for an endpoint are not amenable to modeling, the POD will be the statistically-derived study NOAEL. Since the NOAEL for misaligned sternebrae is 1,010 ppm and is lower than the $BMCL_{05}$ of 2,246 ppm for decreased mean fetal body weight, 1,010 ppm will be used as the most appropriate POD from the Schwetz et al. (1991) study.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

When humans were exposed to MEK in the key study, the exposure durations were 4 h. Mild sensory irritation is often assumed to be a concentration-dependent effect so the concentration at the 1-h exposure duration was assumed to be equal to the concentration at the 4-h exposure duration. The exposure concentration at the 1-h exposure duration was also conservatively assumed to be equal to the exposure concentration for a 4-h exposure duration. In addition, since a free-standing NOAEL was used, there is not adequate information on the dose-response relationship to perform an informed, adequate duration adjustment.

Since the POD from the supporting animal study is derived from a developmental endpoint, the exposure duration will not be adjusted from the 7-h exposure duration to 1 h according to ESL Guidelines (TCEQ 2006) due to potential sensitive windows of exposure. In addition, since the MOA is not known, it is unknown whether both concentration and duration play a role in developmental toxicity.

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Because MEK is rapidly transferred between the lungs and blood and developmental effects are systemic, MEK is considered a Category 3 gas (USEPA 1994b). For Category 3 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

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

where:

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

The blood:gas (air) partition coefficient ($H_{b/g}$) value for MEK in humans (H) was estimated to be 125 (Fiserova-Bergerova and Diaz 1986), whereas in rats (A) this value ranged from 138 to 139 (Thrall et al. 2002). Where the ratio of animal to human blood:air partition coefficients ($(H_{b/g})_A/(H_{b/g})_H$) is greater than one, a default value of one is used for the ratio (USEPA 1994).

Developmental effects in mice

$$\begin{aligned} \text{POD}_{\text{HEC}} &= \text{POD}_{\text{ADJ}} \times \text{RGDR} \\ &= 1,010 \text{ ppm} \times 1 \\ &= 1,010 \text{ ppm} \end{aligned}$$

3.1.6 Adjustments of the POD_{HEC}

A freestanding NOAEL in humans and developmental effects in rats are noncarcinogenic effects. The default for noncarcinogenic effects is to determine a POD and apply uncertainty factors (UFs) to derive a ReV (i.e., assume a nonlinear MOA).

3.1.6.1 Neurological Effects and Sensory Irritation in Humans (Dick et al. 1992)

The following UFs were applied to the POD_{HEC} of 200 ppm for neurological effects and sensory irritation in humans: 10 for intraspecies variability (UF_H) and 1 for database uncertainty (UF_D); the total $\text{UF} = 10$. A full UF_H of 10 was used to account for intraspecies variability. A database UF_D of 1 was used because the overall acute toxicological database for MEK is high.

$$\begin{aligned} \text{acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_D) \\ &= 200 \text{ ppm} / (10 \times 1) \\ &= 200 \text{ ppm} / 10 \\ &= 20 \text{ ppm} \end{aligned}$$

3.1.6.2 Developmental Effects in Mice (Schwetz et al. 1991)

The following UFs were applied to the POD_{HEC} of 1,010 ppm for developmental effects in rats: 10 for UF_H , 3 for UF_A , and 1 for UF_D , the total $\text{UF} = 30$. A full UF_H of 10 was used to account for intraspecies variability. A UF_A of 3 was used for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted, which accounts for toxicokinetic differences but not toxicodynamic differences. A UF_L was not applicable because a NOAEL was used as the POD. The key study was well-designed and tested several exposure concentrations over a reasonable range that included maximum tolerated concentrations for both dams and fetuses, and a second study in rats produced similar developmental results. A database UF_D of 1 was used because the quality of the key study is high and the confidence in the acute database is high.

$$\begin{aligned} \text{acute ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_A \times \text{UF}_D) \\ &= 1,010 \text{ ppm} / (10 \times 3 \times 1) \\ &= 1,010 \text{ ppm} / 30 \\ &= 34 \text{ ppm} \end{aligned}$$

3.1.7 Critical Effect

Neurological effects and sensory irritation are the critical health effects that the acute ReV is designed to protect against.

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

The resulting 1-h acute ReV is 20 ppm (59 mg/m³) or 20,000 ppb (59,000 µg/m³) based on the Dick et al. (1992) study. 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 6,000 ppb (18,000 µg/m³) (Table 2).

Table 6. Derivation of the Acute ReV and ^{acute}ESL	
Study	Dick et al. (1992)
Study Population	13 male; 11 female human volunteers
Study Quality	High
Exposure Methods	Inhalation Chamber , exposure to 200 ppm
POD _{HEC}	200 ppm, free standing NOAEL
Critical Effects	Neurological effects; sensory irritation
Exposure Duration	4 h
Extrapolation to 1 h	No adjustment made
POD _{HEC ADJ} (1 h)	200 ppm
Total UFs	10
<i>Interspecies UF</i>	Not Applicable (N/A)
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	N/A
<i>Incomplete Database UF</i>	1
<i>Database Quality</i>	High
acute ReV [1 h] (HQ = 1)	59,000 µg/m³ (20,000 ppb)
^{acute}ESL [1 h] (HQ = 0.3)	18,000 µg/m³ (6,000 ppb)

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

MEK's odor has been described as sweet and sharp with the hedonic tone described as neutral to unpleasant (Leonardos et al. 1969; Hellman and Small 1974). Published odor detection threshold values that met the criteria accepted by AIHA, USEPA, and TCEQ (AIHA 1989; USEPA 1992 and TCEQ 2006) are summarized in Table 7.

Investigator	Odor Detection Threshold Value	Quality Level
May (1966)	236,000 $\mu\text{g}/\text{m}^3$ (80,000 ppb)	3
Dravnieks (1974)	737,500 $\mu\text{g}/\text{m}^3$ (250,000 ppb)	3
Hellman & Small (1974)	17,110 $\mu\text{g}/\text{m}^3$ (5,800 ppb)	3
van Doorn et al. (2002)	295 $\mu\text{g}/\text{m}^3$ (100 ppb)	2
Nagata (2003)	1,298 $\mu\text{g}/\text{m}^3$ (440 ppb)	1
^{acute}ESL_{odor}	1,300 $\mu\text{g}/\text{m}^3$ (440 ppb)	

Five studies listed as acceptable sources for odor threshold values in Appendix B of the guidelines (TCEQ 2006) were identified: May (1966), Dravnieks (1974), Hellman & Small (1974), van Doorn et al. (2002), and Nagata (2003). A 50% odor detection threshold value of 1,300 $\mu\text{g}/\text{m}^3$ (440 ppb) was reported for MEK by Nagata (2003) utilizing the Japanese triangular odor bag method. According to the interim guidelines for setting odor-based effects screening levels (TCEQ 2010), odor detection values defined as the highest quality level of odor thresholds (Level 1) will be considered first in setting the ^{acute}ESL_{odor} values. If no Level 1 values are available, Level 2 quality data will be considered. If no Level 1 or 2 odor thresholds are available, then Level 3 quality data that meet the criteria from the AIHA (1989) and USEPA (1992) may be used. The odor detection thresholds reported by Nagata (2003) were determined by the standardized methods of measuring odor; the odor detection value is defined as Level 1 (TCEQ 2010). The odor threshold reported by van Doorn et al. (2002) is defined as Level 2 quality data. The odor thresholds reported by May (1966), Dravnieks (1974) and Hellman and Small (1974) (Table 7), however, are defined as Level 3 quality data. Therefore, only the standardized odor detection threshold determined by Nagata (2003) was used to set the ^{acute}ESL_{odor}. Accordingly, the ^{acute}ESL_{odor} for MEK was set at the 50% odor detection threshold of 1,300 $\mu\text{g}/\text{m}^3$ (440 ppb) determined by Nagata (2003).

3.2.2 Vegetative Effects

Three vegetative studies were identified and summarized by IPCS (1993) however, an ^{acute}ESL_{veg} was not developed because data were not sufficient to calculate an air concentration.

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

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

- ^{acute}ESL_{odor} = 1,300 $\mu\text{g}/\text{m}^3$ (440 ppb)
- ^{acute}ESL = 18,000 $\mu\text{g}/\text{m}^3$ (6,000 ppb)
- acute ReV = 59,000 $\mu\text{g}/\text{m}^3$ (20,000 ppb)

For the evaluation of ambient air monitoring data, the ^{acute}ESL_{odor} is lower than the acute ReV (Table 1), although both values may be used for the evaluation of air data. The short-term ESL for air permit evaluations is the ^{acute}ESL_{odor} of 1,300 $\mu\text{g}/\text{m}^3$ (440 ppb) as it is lower than the ^{acute}ESL (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

This section is based on a review of current literature as well as background readings in USEPA (2003) which describe in detail the chronic toxicity of MEK. The TD will use key studies from USEPA (2003) as well as data from the most recent publications, if available, to derive chronic toxicity factors for MEK. The DSD is a summary of the key and supporting studies used by the TD to derive toxicity values.

4.1.1 Physical/Chemical Properties and Key Study

4.1.1.1 Physical/Chemical Properties

Physical/chemical properties of MEK have been previously discussed in Chapter 3, Section 3.1.1. Also, the main chemical and physical properties of MEK are summarized in Table 3.

4.1.1.2 Human Studies

Several occupational studies examined the effects of chronic exposure to MEK: (Smith and Mayers 1944), (Freddi et al. 1982), (Oleru and Onyekwere 1992), and (Mitran et al. 1997). Health effects observed in each of these studies are discussed in USEPA (2003) and summarized as follows:

- Smith and Mayers (1944) reported numbness of fingers and arms and dermatoses following chronic exposure to MEK in workers in an American factory that produced coated fabric. The concentration of MEK was estimated to be 300–600 ppm (as cited in WHO, 1992).
- In Freddi et al. (1982), 51 Italian workers were chronically exposed to MEK. Reports indicate that MEK exposure was associated with slightly, but not statistically significant, reduced nerve conduction velocities (distal axonopathy) and other symptoms such as headache, loss of appetite and weight, gastrointestinal upset, dizziness, dermatitis, and muscular hypotrophy, but no clinically recognizable neuropathy (as cited in WHO, 1992).
- Oleru and Onyekwere (1992) examined the relative impacts of exposures to MEK and other chemicals for four operations (plastic, leather, rubber, and tailoring) at a Nigerian shoe factory. Neurological effects were reported. However, association of the reported neurological effects with MEK is problematic because workers were exposed to multiple solvents (including hexacarbon solvents whose neurotoxicity is reportedly intensified by MEK) concurrently. Additionally, because MEK concentrations in the shoe factory were not measured, the absence of measured airborne concentrations of MEK limits the utility of the data for use in dose-response assessment.

The Smith and Mayers (1944) and Freddi et al. (1982) studies are not used since the exposure concentration and duration are uncertain. The Oleru and Onyekwere (1992) study is not used

because exposure concentration data were not provided, and there was concurrent exposure to multiple solvents. These studies could not be used in a dose-response assessment.

Another epidemiological study where exposure to MEK alone was reported for one of the investigated groups was a study conducted by Mitran et al. (1997). In this study, Romanian workers were exposed to measured concentrations of 149 - 342 mg/m³ MEK during an 8-h shift. Exposed workers showed increased proximal and distal latencies in the median nerve, increased proximal and distal latencies and decreased proximal amplitude in the ulnar nerve, increased proximal latency and decreased distal amplitude in the peroneal nerve, and statistically significant reductions in nerve conduction velocity, but according to USEPA (2003):

“The report does not provide information regarding important methodological details including: (1) criteria for selecting and matching the exposed and control workers (important confounding variables that can influence nerve conduction include the type of work [e.g., office vs. physical work], alcohol and tobacco consumption habits, and height and weight); (2) protocols for assessing exposure levels experienced by the workers; and (3) protocols used in the nerve conduction tests (e.g., it is not clear whether the exposed and control subjects were tested at the same location and time and under the same environmental conditions).”

USEPA (2003) states that human case reports and the epidemiology studies discussed above provide limited and equivocal evidence that repeated exposure to MEK in the workplace increases the hazard for persistent neurological impairment and are not adequate for a dose-response assessment. Therefore, an animal study was used to develop the chronic ReV.

4.1.1.3 Animal Studies

The key animal study was a subchronic study conducted by Cavender et al. (1983) in rats. There were several animal studies in different species that were located but not considered because of low numbers of animals, one exposure concentration, or poor descriptions: LaBelle and Brieger (1955); Saida et al. (1976); Takeuchi et al. (1983); Garcia et al. (1978); Geller et al. (1979); Couri et al. (1974); Altenkirch et al. (1978); and Toftgard et al. (1981), as cited in USEPA (2003). USEPA (2003) states “Well-conducted studies in experimental animals provide no convincing evidence that repeated inhalation exposure to MEK itself (at much higher exposure levels than those in the workplace) is capable of producing persistent neurological effects.”

Key Study (Cavender et al. 1983)

MEK inhalation exposures in rats have been reported by Cavender et al. (1983). Male and female Fischer 344 rats (15 rats per sex per concentration level) were exposed to 0 ppm (air) and to analytical concentrations of 1,254, 2,518, or 5,041 ppm MEK 6 h/day, 5 days per week for 90 days. General histological examinations were performed on 10 animals from each exposure group and neuropathologic examinations were performed on the remaining five animals from each exposure group. Chronic respiratory disease was observed in rats of all groups (both MEK-exposed and control). A high prevalence of nasal inflammation was observed in all exposure

groups and in controls. It is suggested by the authors that the pulmonary lesions were a result of mycoplasma infection, although no infectious agent was cultured.

The only statistically significant changes were increased relative kidney and liver weight. Increased relative kidney and liver weights were observed in rats exposed to 5,041 ppm MEK, but not at 2,518 ppm. Female rats exposed at the highest level also exhibited an increase in serum alkaline phosphatase levels. These effects were not considered adverse since there were no corresponding histopathological changes (USEPA 2003). The free-standing NOAEL of 5,041 ppm was used as the POD. It is not clear what effect appears first as exposure levels increase, although upper respiratory tract irritation was noted in rats exposed to 10,000 ppm MEK, but not to 6,000 ppm MEK (Altenkirch, Stoltenburg, and Wagner 1978). In this study animals were co-exposed to n-hexane/MEK and MEK only. The initial concentration of 10,000 ppm had to be decreased to 6,000 ppm within a few days in the group exposed to MEK only because of severe irritation of the upper respiratory tract. Rats exposed to MEK only did not develop any obvious motor impairment up to the 7th week, when all animals died from bronchopneumonia without neurological symptoms. The authors did not comment on how bronchopneumonia related to MEK exposure.

Portal-of-entry effects were not reported consistently at lower concentrations or shorter exposure durations:

- Dick et al. (1984, 1989, 1992) did not find any reported effects related to irritation from MEK at exposures up to 200 ppm for up to 4 h;
- in an earlier study involving few subjects and unclear exposure conditions, exposure to 300 ppm MEK was reported to be intolerable (Nelson et al. 1943); and
- respiratory irritation was not reported in dams exposed to 3,000 ppm MEK, 7 h/day (GD 6–15) (Schwetz et al. 1974, 1991; Deacon et al. 1981).

In summary, a subchronic inhalation study in rats (Cavender et al. 1983) found no neurological effects after exposure to MEK at a free-standing NOAEL of 5,041 ppm, but did report slightly decreased liver and kidney weights that were not considered adverse. At a higher concentration (10,000 ppm), upper respiratory irritation was noted in rats exposed to MEK for a few days (Altenkirch et al. 1978), which may indicate that upper respiratory tract irritation would most likely occur if rats were exposed to higher concentrations of MEK.

4.1.2 Mode of Action and Dose Metric

The MOA for neurological effects caused by MEK is not known, so a threshold, nonlinear dose-response relationship is assumed. Exposure concentration of the parent chemical will be used as the default dose metric since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available.

4.1.3 PODs for Key Study and Dosimetric Adjustments

In the key study (Cavender et al. 1983), no significant adverse effects were observed in rats. The POD_{animal} is equal to the free-standing NOAEL of 5,041 ppm.

4.1.3.1 Default Exposure Duration Adjustments

The animals used in this study were exposed to MEK for 6 h/per day, 5 days per week for 90 days. It was necessary to adjust the study POD_{animal} from a discontinuous animal exposure scenario to a continuous exposure scenario POD_{ADJ} by using the following equation:

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

where:

D = Exposure duration, h/day

F = Exposure frequency, days per week

$$POD_{\text{ADJ}} = 5,041 \text{ ppm} \times (6/24 \text{ h}) \times (5/7 \text{ d})$$

$$POD_{\text{ADJ}} = 900.2 \text{ ppm}$$

4.1.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Neurotoxicity, the health effect of concern, is a remote effect so the default dosimetry adjustment from animal-to-human exposure is conducted as a Category 3 vapor. For Category 3 vapors, the default dosimetric adjustment from animal-to-human exposure is:

$$POD_{\text{HEC}} = POD_{\text{ADJ}} \times [(H_{\text{b/g}})_{\text{A}} / (H_{\text{b/g}})_{\text{H}}]$$

where:

$H_{\text{b/g}}$ = ratio of the blood:gas partition coefficient

A = animal

H = human

The blood:gas (air) partition coefficient ($H_{\text{b/g}}$) value for MEK in humans (H) was estimated to be 125 (Fiserova-Bergerova and Diaz, 1986), whereas in rats (A) this value ranged from 138 to 139 (Thrall et al. 2002). Where the ratio of animal to human blood:air partition coefficients ($(H_{\text{b/g}})_{\text{A}}/(H_{\text{b/g}})_{\text{H}}$) is greater than one, a default value of one is used for the ratio (USEPA 1994).

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

$$= 900.2 \text{ ppm} \times 1$$

$$= 900.2 \text{ ppm}$$

4.1.4 Adjustments of the POD_{HEC}

Toxic endpoints were not observed in Cavender et al. (1983). A POD_{ADJ} based on a free-standing NOAEL was used as the POD and UFs were applied to derive a ReV (i.e., assume a nonlinear MOA for a noncarcinogenic endpoint). The following uncertainty factors (UFs) were applied to

the POD_{ADJ} of 900.2 ppm: 10 for UF_H , 3 for UF_A , 3 for UF_{Sub} , and 3 for UF_D , for a total UF of 300.

- An UF_H of 10 was used to account for human variability;
- An UF_A of 3 was used because default dosimetric adjustments from animal-to-human exposure were conducted, which account for toxicokinetic differences but not toxicodynamic differences;
- An UF_{Sub} of 3 rather than 10 was used to account for the use of a subchronic study. The exposure duration was likely long enough to observe chronic effects but it is unknown; and
- A database UF_D of 3 was used because of the absence of a two-generation inhalation reproductive/ developmental study. A full UF_D of 10 was not used because a two-generation reproductive/developmental study conducted after exposure of rats to butanol in drinking water (Cox et al. 1975 as discussed in USEPA 2003) was available. Butanol is a premetabolite of MEK that is rapidly converted to MEK. The Cox et al. (1975) study “indicated the administration of 2-butanol in drinking water at concentrations as high as 3% did not affect reproductive performance in rats (with the possible exception of male rat copulatory success), but produced maternal toxicity accompanied by developmental effects at the highest exposure level.”

$$\begin{aligned}
 \text{chronic ReV} &= \text{POD}_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D) \\
 &= 900.2 \text{ ppm} / (10 \times 3 \times 3 \times 3) \\
 &= 900.2 \text{ ppm} / 300 \\
 &= 3 \text{ ppm} \\
 &= 3,000 \text{ ppb}
 \end{aligned}$$

The quality of the Cavender et al. (1983) study is high. The overall chronic database for MEK is medium. The chronic ReV is 3,000 ppb based on this study.

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

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 8,800 $\mu\text{g}/\text{m}^3$ (3,000 ppb). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 2,600 $\mu\text{g}/\text{m}^3$ (900 ppb).

Table 8. Derivation of the Chronic ReV and ^{chronic}ESL	
Study	Cavender et al. (1983)
Study Population	Fischer 344 rats: 15 males, 15 females per concentration group
Study Quality	High
Exposure Method	Inhalation Chamber at 0, 1,254, 2,518, or 5,041 ppm MEK
Critical Effects	No adverse effects observed
POD	5,041 (free-standing NOAEL)
Exposure Duration	6/h/day, 5 days/week for 90 days (Sub-chronic)
Extrapolation to continuous exposure (POD _{ADJ})	900.2 ppm
POD _{HEC}	900.2 ppm
Total UFs	300
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	N/A
<i>Subchronic to chronic UF</i>	3
<i>Incomplete Database UF</i>	3
<i>Database Quality</i>	Medium
Chronic ReV (HQ = 1)	8,800 µg/m³ (3,000 ppb)
^{chronic} ESL _{nonlinear(nc)} (HQ = 0.3)	2,600 µg/m³ (900 ppb)

4.1.6 Comparison of TCEQ's Chronic ReV to USEPA's Chronic Reference Concentration

The current USEPA reference concentration (RfC) of 5 mg/m³ is based on a developmental study conducted by Schwetz et al. (1991) where the exposure concentration corresponding to a 10% extra risk of misaligned sternalbrae in CD-1 mice was selected as the POD. The current RfC is based on a BMD approach, rather than the NOAEL/LOAEL approach, and a combined UF of 300 (3 for UF_A, 10 for UF_H, and 10 for UF_D). The TD recognizes that reproductive/developmental effects may be caused by only a single day's exposure that occurred at a critical time during gestation; therefore, a developmental study is not used to derive a chronic value (TCEQ 2006). The chronic ReV of 8.8 mg/m³, which is based on an exposure concentration that did not result in adverse effects (Cavender et al. 1983), is approximately 1.8 times the current RfC.

4.2 Carcinogenic Potential

USEPA (2003) provides the following information in Section 4.6 *Weight-Of-Evidence Evaluation and Cancer Characterization*:

“Under EPA’s draft revised cancer guidelines (USEPA 1999), “data are inadequate for an assessment of human carcinogenic potential” for MEK, because studies of humans chronically-exposed to MEK are inconclusive, and MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes. The majority of short-term genotoxicity testing of MEK has demonstrated no activity, and SAR [structure-activity relationship] analysis suggests that MEK is unlikely to be carcinogenic.”

Since there are no human or animal studies or other data indicating that MEK has carcinogenic potential, a chronic carcinogenic value was not developed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV 8,800 $\mu\text{g}/\text{m}^3$ (3,000 ppb)
- ^{chronic}ESL_{nonlinear (nc)} 2,600 $\mu\text{g}/\text{m}^3$ (900 ppb)

The chronic ReV of 8,800 $\mu\text{g}/\text{m}^3$ (3,000 ppb) will be used for the evaluation of ambient air monitoring data (Table 1). The ^{chronic}ESL_{nonlinear (nc)} of 2,600 $\mu\text{g}/\text{m}^3$ (900 ppb) is the long-term ESL used for air permit reviews (Table 2). The ^{chronic}ESL_{nonlinear (nc)} is not used to evaluate ambient air monitoring data.

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Appendix A Benchmark Dose Modeling

Table A-1. Mean Fetal Body Weight (mice) and Standard Deviation ^a (Mast et al. 1989 and Schwetz et al. 1991)			
Concentration (ppm)	# of Litter	Fetal Weight: mean of litter means (g)	Standard Deviation (SD)
3020	28	1.29	0.08
1010	26	1.33	0.07
398	23	1.35	0.06
0	26	1.35	0.07

^a significantly correlated with exposure concentration, p<0.05

Table A-2. Benchmark Dose Modeling Results Fetal Body Weight							
BMDS Model	AIC	Goodness of fit p-value	Scaled Residual	BMC _{1 SD}	BMCL _{1 SD}	BMC ₀₅	BMCL ₀₅
Linear Model	-440.9	0.9038	< 2	3338.74	2272.53	3248.11	2246.09
Polynomial Model	-438.2	0.6552	< 2	3329.7	1560.76	3244.21	1515.70
Power Model- Restricted	-438.2	0.6665	< 2	3342.92	2274.76	3257.41	2248.23
Power Model – Unrestricted	-438.2	0.6665	< 2	3342.92	2011.07	3257.41	1972.29

Concentration (ppm)	# of Litters	Incidence (#/total # of fetuses)	Mean % of misaligned sternebrae/ litter (mean ± SD)
3020	28	58/323	17.5 ± 14.9
1010	26	49/291	17.4 ± 16.7
398	23	27/260	9.8 ± 11.2
0	26	31/310	9.7 ± 10.4

^a significantly correlated with exposure concentration, p<0.05

BMDS Model	AIC	Goodness of fit p-value	Scaled Residual	BMC ₀₅	BMCL ₀₅
Polynomial Model^b	642.1	0.1252	< 2	1821.21	689.631^b
Power Model-Restricted	645.3	0.02306 ^a	---	---	---
Power Model – Unrestricted	644.8	0.02523 ^a	---	---	---

^a Failed test 4 (i.e., goodness of fit p-value implied rejection at the 5% significance level)

^b Dose-response curve was nonmonotonic

**Fetal Weight BMDL
Linear Model**

=====
Polynomial Model. (Version: 2.13; Date: 04/08/2008)
Input Data File: C:\USEPA\BMDS2\Temp\tmp39C.(d)
Gnuplot Plotting File: C:\USEPA\BMDS2\Temp\tmp39C.plt
Fri Mar 27 09:08:26 2009
=====

BMDS Model Run
~~~~~

The form of the response function is:

$$Y[\text{dose}] = \text{beta}_0 + \text{beta}_1 * \text{dose} + \text{beta}_2 * \text{dose}^2 + \dots$$

Dependent variable = Weight  
Independent variable = DOSE  
rho is set to 0  
Signs of the polynomial coefficients are not restricted  
A constant variance model is fit

Total number of dose groups = 4  
Total number of records with missing values = 0  
Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha = 0.0050202  
rho = 0 Specified  
beta\_0 = 1.35314  
beta\_1 = -2.09075e-005

Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -rho

have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

|        |           |           |           |
|--------|-----------|-----------|-----------|
|        | alpha     | beta_0    | beta_1    |
| alpha  | 1         | -5.9e-010 | -6.9e-010 |
| beta_0 | -5.9e-010 | 1         | -0.7      |
| beta_1 | -6.9e-010 | -0.7      | 1         |

Parameter Estimates

| Variable | Estimate      | Std. Err.    | 95.0% Wald Confidence Interval |                   |
|----------|---------------|--------------|--------------------------------|-------------------|
|          |               |              | Lower Conf. Limit              | Upper Conf. Limit |
| alpha    | 0.00483473    | 0.000673703  | 0.0035143                      | 0.00615516        |
| beta_0   | 1.3529        | 0.00958809   | 1.33411                        | 1.37169           |
| beta_1   | -2.08259e-005 | 5.75863e-006 | -3.21126e-005                  | -9.5392e-006      |

Table of Data and Estimated Values of Interest

| Dose | N  | Obs Mean | Est Mean | Obs Std Dev | Est Std Dev | Scaled Res. |
|------|----|----------|----------|-------------|-------------|-------------|
| 3020 | 28 | 1.29     | 1.29     | 0.08        | 0.0695      | -0.000339   |
| 1010 | 26 | 1.33     | 1.33     | 0.07        | 0.0695      | -0.137      |
| 398  | 23 | 1.35     | 1.34     | 0.06        | 0.0695      | 0.372       |
| 0    | 26 | 1.35     | 1.35     | 0.07        | 0.0695      | -0.213      |

Model Descriptions for likelihoods calculated

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \text{Sigma}(i)^2$$

Model A3:  $Y_{ij} = \text{Mu}(i) + e(ij)$

$$\text{Var}\{e(ij)\} = \text{Sigma}^2$$

Model A3 uses any fixed variance parameters that were specified by the user

Model R:  $Y_i = \text{Mu} + e(i)$

$$\text{Var}\{e(i)\} = \text{Sigma}^2$$

#### Likelihoods of Interest

| Model         | Log(likelihood)   | # Param's | AIC                |
|---------------|-------------------|-----------|--------------------|
| A1            | 223.195553        | 5         | -436.391107        |
| A2            | 224.250451        | 8         | -432.500903        |
| A3            | 223.195553        | 5         | -436.391107        |
| <b>fitted</b> | <b>223.094409</b> | <b>3</b>  | <b>-440.188818</b> |
| R             | 216.938065        | 2         | -429.876131        |

#### Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?  
(A2 vs. R)

Test 2: Are Variances Homogeneous? (A1 vs A2)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

(Note: When  $\rho=0$  the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

| Test   | $-2*\log(\text{Likelihood Ratio})$ | Test df | p-value |
|--------|------------------------------------|---------|---------|
| Test 1 | 14.6248                            | 6       | 0.02338 |
| Test 2 | 2.1098                             | 3       | 0.5499  |
| Test 3 | 2.1098                             | 3       | 0.5499  |
| Test 4 | 0.202289                           | 2       | 0.9038  |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels  
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

### Benchmark Dose Computation

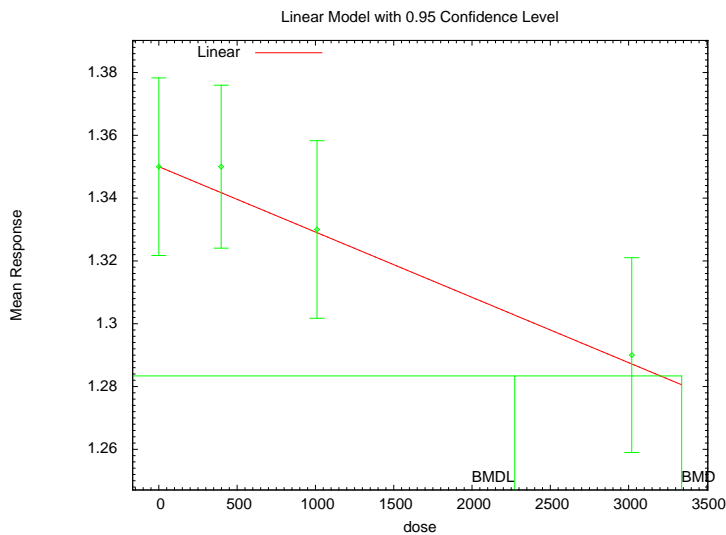
Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3338.74

BMDL = 2272.53



Benchmark Dose Computation

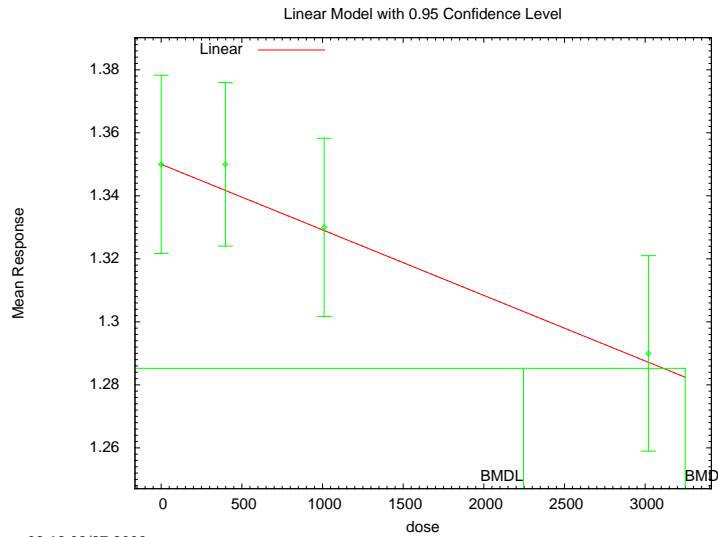
Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 3248.11

BMDL = 2246.09



**Misaligned Sternebrae  
Polynomial Model**

=====  
Polynomial Model. (Version: 2.13; Date: 04/08/2008)  
Input Data File: C:\USEPA\BMDS2\Temp\tmp23.(d)  
Gnuplot Plotting File: C:\USEPA\BMDS2\Temp\tmp23.plt  
Wed May 20 14:57:58 2009  
=====

BMDS Model Run  
~~~~~

The form of the response function is:

$$Y[\text{dose}] = \text{beta}_0 + \text{beta}_1 * \text{dose} + \text{beta}_2 * \text{dose}^2 + \dots$$

Dependent variable = Mean

Independent variable = DOSE

Signs of the polynomial coefficients are not restricted

The variance is to be modeled as $\text{Var}(i) = \exp(\text{lalpha} + \log(\text{mean}(i)) * \text{rho})$

Total number of dose groups = 4

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha = 5.22663
rho = 0
beta_0 = 8.49099
beta_1 = 0.00998146
beta_2 = -2.30722e-006

Asymptotic Correlation Matrix of Parameter Estimates

lalpha rho beta_0 beta_1 beta_2

lalpha	1	-0.99	-0.0046	-0.085	0.12
rho	-0.99	1	0.004	0.091	-0.13
beta_0	-0.0046	0.004	1	-0.64	0.54
beta_1	-0.085	0.091	-0.64	1	-0.97
beta_2	0.12	-0.13	0.54	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
lalpha	1.52578	1.4015	-1.22111	4.27267
rho	1.3938	0.539237	0.336912	2.45068
beta_0	8.9724	1.85422	5.33819	12.6066
beta_1	0.00972761	0.00505155	-0.00017325	0.0196285
beta_2	-2.35811e-006	1.61726e-006	-5.52788e-006	8.11649e-007

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	26	9.7	8.97	10.4	9.89	0.375
398	23	9.8	12.5	11.2	12.4	-1.03
1010	26	17.4	16.4	16.7	15.1	0.341
3020	28	17.5	16.8	14.9	15.3	0.227

Model Descriptions for likelihoods calculated

Model A1: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3: $Y_{ij} = \mu(i) + e(ij)$
 $\text{Var}\{e(ij)\} = \exp(\alpha + \rho \cdot \ln(\mu(i)))$
 Model A3 uses any fixed variance parameters that were specified by the user

Model R: $Y_i = \mu + e(i)$
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-318.631371	5	647.262742
A2	-314.751628	8	645.503255
A3	-314.884235	6	641.768470
fitted	-316.059848	5	642.119696
R	-322.726405	2	649.452810

Explanation of Tests

- Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
 - Test 2: Are Variances Homogeneous? (A1 vs A2)
 - Test 3: Are variances adequately modeled? (A2 vs. A3)
 - Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
- (Note: When $\rho=0$ the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	$-2 \cdot \log(\text{Likelihood Ratio})$	Test df	p-value
Test 1	15.9496	6	0.01403
Test 2	7.75949	3	0.05125
Test 3	0.265215	2	0.8758
Test 4	2.35123	1	0.1252

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

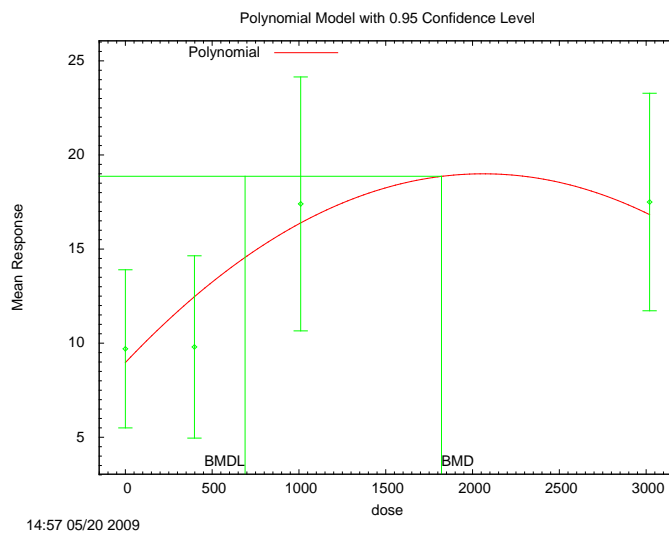
Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 1821.21

BMDL = 689.631



Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 51.5014

BMDL = 28.3952

