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Methacrolein

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Revision History

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Revised DSD March 14, 2014: The DSD was revised based on updated guidance from USEPA (2012) (i.e., for the chronic reference value, dosimetric adjustments were performed as a Category 1 vapor based on updated recommendations on animal-to-human dosimetric adjustments in USEPA (2012): the default regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) is 1).

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADH	aldehyde dehydrogenase
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
$^{\circ}$C	degrees Celsius centigrade
BMR	benchmark response
bw	body weight
ConA	Concanavalin A
CRO	crotonaldehyde
DSD	development support document
EC_{50}	Effective concentration at a 50% response level
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level

Acronyms and Abbreviations	Definition
$^{chronic}ESL_{generic}$	chronic health-based Effects Screening Level for chemicals not meeting minimum database requirements
GC	gas chromatography
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IC_{50}	inhibitory concentration at a 50% response level
IL	interleukin
IP	intraperitoneal
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LC_{50}	concentration causing lethality in 50% of test animals
LD_{50}	dose causing lethality in 50% of test animals
LPS	lipopolysaccharide
LOAEL	lowest-observed-adverse-effect-level
LTD	limited toxicity data
MW	molecular weight
µg	microgram
$µg/m^3$	micrograms per cubic meter of air
mg	milligrams

Acronyms and Abbreviations	Definition
mg/m^3	milligrams per cubic meter of air
min	minute
MOA	mode of action
n	number
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
RD_{50}	50% reduction in respiration rate
ReV	reference value
ROS	reactive oxygen species
RP_{GM}	geometric mean of relative potency
SA	surface area
SCOEL	Scientific Committee on Occupational Exposure Limits
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor

Acronyms and Abbreviations	Definition
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
V_E	minute volume

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of methacrolein. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on methacrolein's physical/chemical data.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV	**Short-Term Health** 53 µg/m^3 (19 ppb)	**Critical Effect:** Increase in blink frequency in healthy male humans
$^{acute}ESL_{odor}$	**Odor** 24 µg/m^3 (8.5 ppb)	50% detection threshold, acrid odor
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**Long-Term Health** 8.1 µg/m^3 (2.9 ppb)	**Critical Effect:** Upper respiratory tract effects in Sprague-Dawley rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	No data found
$^{chronic}ESL_{veg}$	- - -	No data found

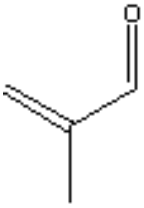
Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	**Short-Term ESL for Air Permit Reviews** 16 µg/m^3 (5.7 ppb) [a]	**Critical Effect:** Increase in blink frequency in healthy male humans
$^{acute}ESL_{odor}$	24 µg/m^3 (8.5 ppb)	50% detection threshold, acrid odor
$^{acute}ESL_{veg}$	- - -	Insufficient data
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**Long-Term ESL for Air Permit Reviews** 2.4 µg/m^3 (0.87 ppb) [b]	**Critical Effect:** Upper respiratory tract effects in Sprague-Dawley rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	No data found
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Based on the acute ReV of 53 µg/m^3 (19 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[b] Based on the chronic ReV of 8.1 µg/m^3 (2.9 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_4H_6O	AEGL 2008
Chemical Structure		ChemFinder
Molecular Weight	70.09 g/mol	AEGL 2008
Physical State	Liquid	AEGL 2008
Color	Colorless	AEGL 2008
Odor	acrid	Pedersen and Sehested 2001
CAS Registry Number	78-85-3	AEGL 2008
Synonyms	2-methylacrolein; methacrylic aldehyde; isobutenal; 2-methylpropenal; 2-methyl-2-propenal	AEGL 2008
Solubility in water	59,000 mg/L	AEGL 2008
Log K_{ow}	Not available	
Vapor Pressure	155 mm Hg @ 25º C	AEGL 2008
Vapor Density (air = 1)	2.4	AEGL 2008
Density (water = 1)	0.8	AEGL 2008
Melting Point	-81º C	AEGL 2008
Boiling Point	68.4º C	AEGL 2008
Conversion Factors	1 ppm = 2.8 mg/m^3 1 mg/m^3 = 0.36 ppm	AEGL 2008

Chapter 2 Major Sources and Uses

Methacrolein (MET) is an intermediate in the production of copolymers, resins, methacrylonitrile, and methacrylicic acid (HSDB 2002). Use of MET other than as an intermediate was discontinued when better catalysts became available (AEGL 2008). MET may be present in automobile exhaust, liquid floor wax, and steel protective paints (AEGL 2008). MET can be formed from the reaction of atmospheric isoprene and ozone (Biesenthal et al. 1997) and can be formed in indoor air by oxidation of isoprene by ozone, hydroxide, and nitrate (Atkinson and Arey 2003). It is also released into the air by certain plants, such as sagebrush, which use MET as a chemical defense signal (Kessler et al. 2006).

Chapter 3 Acute Evaluation

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

This section is based on information on MET obtained from AEGL (2008) as well as literature searches beginning from 1980. MET is a sensory/respiratory irritant, affecting mainly the eyes and upper airways.

3.1.1 Physical/Chemical Properties

MET is a colorless liquid with an acrid smell that resembles the smell of ozone when dilute (Pedersen and Sehested 2001). It is very soluble in water, and soluble in ethanol and ether (HSDB 2002). It is highly flammable, with a flash point of 2° C, and may react strongly with oxidizing metals (HSDB 2002). Other physical/chemical properties can be found in Table 2.

3.1.2 Key Studies

3.1.2.1 Human Study

Nøjgaard et al. (2005) conducted a study in humans that examined the effects of MET on eye blink frequency in ten healthy men. The age of the subjects was 43 $\pm$ 10.5 years (mean $\pm$ standard deviation). Eye blink frequency was used to evaluate trigeminal nerve stimulation of the human eye. The men were exposed via an eye cup for 20 minutes (min) to clean air, 89, 189, and 286 parts per billion (ppb) MET (analytical concentration) in their non-dominant eye. Eight minutes prior to and four minutes following each exposure, a baseline blink frequency was measured. The subjects were exposed locally in the non-dominant eye and single blind at 20% relative humidity. Blink frequency was recorded continuously using a video camera while the subjects viewed an educational film. The subjects reported the intensity of the perceived irritation prior to the exposure on a linear scale equally divided into none, weak, moderate, and strong irritation. However, the subjects were also allowed to report intermediate intensities.

Of the 10 subjects, 40-50% experienced “less than weak to weak” eye irritation from any amount of MET, but only the highest concentration of 286 ppb caused a significant increase of 18% in

blink frequency (p = 0.001) when compared to baseline blink frequency (Table 4). The lowest-observed-adverse-effect level (LOAEL) was 286 ppb and the no-observed-adverse-effect level (NOAEL) was 189 ppb.

Table 4 Blink Frequency Changes during MET Exposure (Nøjgaard et al. 2005)

Test Group	**Clean Air (Relative humidity 20%)**	**MET I**	**MET II**	**MET III**
MET (ppb)	-	89 ± 1	189 ± 3	286 ± 2
Subjects who perceived eye irritation	3/10	4/10	5/10	4/10
Perceived intensity	<weak	<weak; weak	<weak; weak	<weak; weak
% Relative change in blink frequency compared to baseline blink frequency	-9	10	8	18 *

* p = 0.001

3.1.2.2 Animal Studies

3.1.2.2.1 Rat Studies

Carpenter et al. (1949) conducted an acute inhalation lethality test of 95 different compounds, including MET. Six male or female Sherman albino rats (specific gender not provided) were exposed for 4 hours (h) to 125 parts per million (ppm) MET (nominal). A specific concentration producing 50% lethality in rats (LC_{50}) was not provided, but a statement was included that MET exposure killed either two, three, or four of the six exposed rats. Based on these results, the authors classified MET as a "definite hazard to life or health from a single vapor exposure."

Coombs et al. (1992), as part of the 2-week study described below, exposed five female and five male Sprague-Dawley rats to 77 ppm MET (analytical) for a single 6-h exposure and observed that one male and three female rats died within day 2, four surviving males were moribund and were sacrificed on day 2, and one female died on day 3. The cause of death was determined to be damage to the respiratory tract.

Coombs et al. (1992) as part of the 2-week plus one day inhalation study (11 total exposures) for 6 h/day, 5 days/week using groups of five male and five female Sprague-Dawley rats and MET concentrations of 0, 5 and 19 ppm (analytical). The study was conducted using Good Laboratory Practices (UK Department of Health 1989). A range of endpoints was evaluated: clinical pathology, hematology, clinical chemistry, organ weights, and macroscopic and microscopic

pathology. During exposure, all MET exposure groups showed signs of closed or half-closed eyes, indicative of exposure to an irritant substance. Red/brown staining around the head was seen in a proportion of rats exposed to 19 ppm from the 2nd week of exposure. None of the animals from the 5 and 19 ppm groups died within the two-week exposure.

The LOAEL for eye irritancy was 5 ppm. No significant effects on hematology or blood chemistry, organ weights, or histopathological changes were noted at 5 ppm. No significant effects on hematology or blood chemistry, or organ weights were noted at 19 ppm. The following effects were observed at 19 ppm: pseudoglandular goblet cell hyperplasia and erosion and/or disorganization of the olfactory epithelium; minimal hyperplasia of the respiratory epithelium; minimal epithelia hyperplasia in the larynx; epithelial hypertrophy in the trachea; and apparent hypertrophy of the zona fasciculate in adrenals (Coombs et al. 1992).

3.1.2.2.2 Mouse Study

In 2000, Larsen and Nielsen conducted an acute inhalation study (1-30 min exposure) using groups of four male BALB/cA mice and MET concentrations of 2.0, 4.4, 6.6, 10.2, 13.1, and 26.3 ppm (analytical). MET exposure caused a dose-dependent decrease in respiratory rate of 10, 30, 40, 50, 55, and 70% at the tested concentrations, respectively. They determined that MET is a 'potent sensory irritant', with an exposure concentration producing a 50% respiratory rate decrease (RD_{50}) of 10.4 ppm and a RD_0 value of 1.3 ppm. Larsen and Nielsen (2000) suggest the main effect of MET is sensory irritation since only a minor airflow limitation occurred in the lower respiratory tract. In addition, no desensitization occurred since the sensory irritation response maintained the same level during exposure.

3.1.2.3 Reproductive/Developmental Studies

No reproductive/developmental studies are available. However, based on the solubility and reactivity of MET and results from the Coombs et al. (1992) and Larsen and Nielsen (2000) studies, significant systemic absorption is not expected.

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

The MOA of MET for sensory irritation is not known, but sensory irritation may result from trigeminal nerve stimulation. Trigeminal nerve fibers respond to a variety of substances and are part of what has traditionally been called the common chemical sense (Hessamedin 2000). In both human and rat studies, exposure to MET resulted in irritation to the eyes (Nøjgaard et al. 2005; Coombs et al. 1992) while respiratory effects were observed at higher concentrations in rats (Coombs et al. 1992). Wolkoff (2005) suggests that MET follows a similar mechanism as that of formaldehyde and acrolein, which stimulate trigeminal nerve endings and may involve the binding of the irritant with a specific receptor (Wolkoff 2005; AEGL 2008). Based on this information, MET may have a similar MOA as a sensory irritant.

Rat studies have shown that MET induces respiratory irritation at higher concentrations than those that produce eye irritation (Coombs et al. 1992). The MOA of MET for cellular damage in the upper respiratory tract is still unclear, but it may result from a mechanism similar to that of other related aldehydes, such as acrolein. These compounds react strongly with sulfhydryl groups (AEGL 2005).

Eye blink frequency, a measure of trigeminal nerve stimulation of the human eye (Nøjgaard et al. 2005), is a minor sensory effect and is considered to be concentration-dependent so exposure concentration of the parent chemical is the most appropriate dose metric. Sensory irritation is assumed to have a threshold or nonlinear MOA.

3.1.4 Point of Departure (POD) for Key Study and Dosimetric Adjustments

The key study was Nøjgaard et al. (2005) which determined a NOAEL in humans of 189 ppb for an increase in eye blink frequency after exposure to MET for 20 min. Eye irritation is the effect that occurs at the lowest concentration in rats as shown in the Coombs et al. (1992) study. A human study that showed mild sensory irritation at lower concentrations than that observed in the rat study is preferred for development of toxicity factors.

The POD_{ADJ} of 1-h exposure duration is equal to the 20-min exposure duration POD because mild sensory irritation is concentration dependent, so the same concentration is assigned to all averaging times. The NOAEL of 189 ppb is used as the human point of departure (POD_{HEC}).

3.1.5 Critical Effect and Adjustments of the POD_{HEC}

The critical effect is mild sensory irritation in humans as indicated by an increase in eye blink frequency with a LOAEL of 286 ppb (Nøjgaard et al. 2005). MET acts as a sensory irritant, a threshold effect with a threshold MOA. The following uncertainty factors (UFs) were applied to the POD_{HEC} of 189 ppb to derive a reference value (ReV): 10 for intraspecies variability (UF_H) and 1 for database uncertainty (UF_D), for a total UF of 10:

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D)$$
$$= 189 \text{ ppb} / (10 \times 1)$$
$$= 18.9 \text{ ppb}$$

- A UF_H of 10 was used to account for variation in sensitivity among members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences. There is no data that indicate that a UF_H larger than 10 is needed to protect children or other sensitive sub groups.

- A UF_D of 1 was used because a study was available in humans investigating sensory irritation in eyes and the respiratory tract (Nøjgaard et al. 2005), and sensory irritation and other health effects in two species of animals (Larsen and Nielsen 2000; Coombs et

al. 1992). Reproductive/ developmental studies were not available, but significant systemic absorption is not expected because of MET's high water solubility and reactivity, and the observation that systemic effects were not observed even at high concentrations (Coombs et al. 1992). Therefore, the confidence in the acute database is medium/high (TCEQ 2006).

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

The resulting 1-h acute ReV is 18.9 ppb. The acute ReV was rounded to two significant figures at the end of all calculations resulting in an acute ReV of 19 ppb (53 µg/m^3). The rounded acute ReV was then multiplied by 0.3 to calculate the 1-h ^{acute}ESL. At the target hazard quotient of 0.3, the 1-h ^{acute}ESL is 5.7 ppb (16 µg/m^3) (Table 5). This acute ReV and ^{acute}ESL are considered to be conservative since they are based on a mild effect in humans (i.e., a slight increase in eye blink frequency).

Table 5 Derivation of the Acute ReV and ^{acute}ESL

Parameter	Summary
Study	Nøgjaard et al. 2005
Study population	Healthy human males
Study quality	Medium
Exposure methods	Exposures via eye cup in nondominant eye at 0, 89, 189, and 286 ppb (analytical)
Critical effect	Increased eye blink frequency
LOAEL	286 ppb
POD	189 ppb (NOAEL)
Exposure duration	20 min
Extrapolation to 1 h	None, minor sensory irritation is concentration dependent (TCEQ 2012)
POD_{ADJ}	189 ppb
POD_{HEC}	189 ppb
Total uncertainty factors (UFs)	10
Interspecies UF	Not applicable
Intraspecies UF	10
LOAEL UF	Not applicable
Incomplete Database UF	1
Database Quality	Medium/high
acute ReV [1 h] (HQ = 1)	**53 µg/m^3 (19 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**16 µg/m^3 (5.7 ppb)**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

The National Institute for Occupational Safety and Health International Chemical Safety Card (NIOSH ICSC 1995) states that MET is a 'colorless liquid with a characteristic odor. Pedersen and Sehested (2001) states MET has an acrid smell at high concentrations but that it resembles the smell of ozone when dilute. The 50% odor detection threshold for MET, as determined by the triangular odor bag method, was 8.5 ppb (24 µg/m^3) (Nagata 2003). The methods used by Nagata (2003) meet the criteria for acceptable odor threshold measurement techniques developed by the American Industrial Hygiene Association and USEPA and are considered a Level 1 odor source as discussed in TCEQ (2012). The value of 24 µg/m^3 (8.5 ppb) reported by Nagata (2003) is the

$^{acute}ESL_{odor}$, and because odor is a concentration-dependent effect, the same 1-h $^{acute}ESL_{odor}$ is assigned to all averaging times.

3.2.2 Vegetation Effects

MET is released into the air by certain plants, such as sagebrush, which use it as a chemical defense signal (Kessler et al. 2006). There is, however, no available data suggesting that MET is harmful or induces negative effects in vegetation or at what concentration negative effects in vegetation occur.

3.3. Short-Term ESL

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

- acute ReV = 53 µg/m^3 (19 ppb)
- $^{acute}ESL$ = 16 µg/m^3 (5.7 ppb)
- $^{acute}ESL_{odor}$ = 24 µg/m^3 (8.5 ppb)

The short-term ESL for air permit evaluations is the health based $^{acute}ESL$ of 16 µg/m^3 (5.7 ppb) as it is slightly lower than the $^{acute}ESL_{odor}$ (Table 1). For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ of 24 µg/m^3 (8.5 ppb) is slightly lower than the acute ReV of 53 µg/m^3 (19 ppb), although both values 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

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 800 µg/m^3 (286 ppb). The $LOAEL_{HEC}$ determined from human studies, where an increase in eye blink frequency (i.e., eye irritation) occurred in some individuals, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. 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. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the observed adverse effect level and the ReV is a factor of 15. (Table 5).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to section 3.1.1.1 and Table 3.

4.1.2 Key Study

This section is based on information on MET obtained from AEGL (2008) as well as literature searches beginning from 1980. As stated previously, MET is a sensory irritant, affecting mainly the eyes and upper airways.

Coombs et al. (1994) conducted a 13-week subchronic inhalation study (6 h/day, 5 days/week) using groups of 10 Sprague-Dawley rats per sex per concentration using whole-body exposure. MET concentrations were 0, 1, 4.9, and 15.3 ppm (analytical) and the study was conducted using Good Laboratory Practices (UK Department of Health 1989). A range of endpoints were evaluated: clinical pathology, hematology, clinical chemistry, organ weights, macroscopic and microscopic pathology. The following effects were observed:

- no adverse effects were observed at 1 ppm;
- half-closed eyes were observed at 4.9 ppm (only for exposure days 1-6) and 15.3 ppm
- salivation (as indicated by wet chins and animals licking the inside of their mouths) was reported occasionally at 15.3 ppm;
- weight gain and food consumption were decreased at 15.3 ppm;
- epithelial inflammatory, atrophic and metaplastic changes in the dorsal meatus and dorsal central septum of the nasal passages and, to a lesser degree, in the larynges of animals was noted at 15.3 ppm; and
- signs of repair and recovery were noted in the respiratory tract of the 15.3 ppm exposed group after a period of recovery.

The subchronic LOAEL for eye irritation was 4.9 ppm and the NOAEL was 1.0 ppm. Half-closed eyes were observed at 4.9 ppm, but only for exposure days 1-6. However, 4.9 ppm was not used as a subchronic NOAEL because acrolein, a reactive aldehyde that is structurally similar to MET, may produce sensory nerve damage after repeated, prolonged exposure leading to “adaptation” (AEGL 2005). MET may also produce adaptation by the same mechanism.

The LOAEL was 15.3 ppm and the NOAEL was 4.9 ppm for the following effects: decreases in weight gain and food intake, epithelial inflammatory, atrophic and metaplastic changes in the dorsal meatus and dorsal central septum of the nasal passages and, to a lesser degree, in the larynges of animals (Coombs et al. 1994). Coombs et al. (1994) states these changes are consistent with the inhalation of an irritating substance.

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

Refer to Section 3.1.2 for a discussion of the MOA for MET. For eye irritation, the dose metric is exposure concentration of the parent chemical and is considered to be concentration dependent. For respiratory tract effects, the MOA of the toxic response is not fully understood and data on other more specific dose metrics is not available, so exposure concentration of the parent chemical will be used as the default dose metric. It is assumed that both concentration and duration play a role for respiratory tract effects. Both sensory irritation and respiratory irritation are considered to have a threshold or nonlinear MOA.

4.1.4 Point of Departure (POD) for Key Study and Dosimetric Adjustments

Based on the Coombs et al. (1994) subchronic rat study, the NOAEL for eye irritation is 1 ppm and for respiratory tract effects is 4.9 ppm.

4.1.4.1 Default Exposure Duration Adjustments

Eye irritation, a mild sensory effect, is concentration-dependent, so a duration adjustment was not necessary:

Increase in eye irritation

POD_{ADJ} = 1 ppm

For the increase in respiratory tract effects, the 6 h/day, 5 days/wk exposure duration was adjusted to a POD_{ADJ} for continuous exposure where both concentration and duration play a role in toxicity for respiratory tract effects:

Increase in respiratory tract effects

POD_{ADJ} = POD x h/24 x d/7
= 4.9 ppm x (6/24) x (5/7)
= 0.875 ppm

4.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

4.1.4.2.1 Increase in eye irritation

Adjustments from animal-to-human exposure for eye irritation are not available. However, the kinetics between animal and humans for direct contact of the eye with MET would not differ, so no toxicokinetic adjustments are deemed necessary. Therefore, the POD_{HEC} is 1 ppm (1000 ppb).

4.1.4.2.2 Increase in respiratory tract effects

The health effects MET produces at lower concentrations are mainly respiratory tract effects in the extrathoracic region of the respiratory tract, so dosimetric adjustments were performed as a Category 1 vapor based on updated recommendations on animal-to-human dosimetric adjustments in USEPA (2012): the default regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) is 1.

For Category 1 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$
$$= 0.875 \text{ ppm} \times 1$$
$$= 0.875 \text{ ppm}$$
$$= 875 \text{ ppb}$$

4.1.5 Critical Effect

The critical effect is an increase in respiratory tract effects in rats exposed to MET (Coombs et al. 1994) because it has the lowest POD_{HEC} of 875 ppb compared to the POD_{HEC} for eye irritation of 1,000 ppb.

4.1.6 Adjustments of the POD_{HEC}

MET acts as a sensory and upper respiratory tract irritant and both of these effects are assumed to have a threshold. Therefore, UFs were applied to the POD_{HEC} to derive a ReV (i.e., assume a threshold MOA).

The following UFs were applied to the POD_{HEC} of 875 ppb for respiratory tract effects: 10 for UF_H, 3 for UF_A, 3 for UF_{Sub}, and 3 for database uncertainty (UF_D), for a total UF = 300:

Increase in respiratory tract effects

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_S \times UF_D)$$
$$= 875 \text{ ppb} / (10 \times 3 \times 3 \times 3)$$
$$= 2.92 \text{ ppb}$$

- A UF_H of 10 was used to account for variation in sensitivity among members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for

human variation including possible child/adult differences. There is no data that indicate that a UF_H larger than 10 is needed to protect children or other sensitive sub groups.

- A UF_A of 3 was used for extrapolation from animals to humans because a default dosimetric adjustment from animal-to-human exposure were conducted (USEPA 2012), which account for toxicokinetic differences but not toxicodynamic differences.

- A UF_{Sub} of 3 was used instead of 10 because a comparison of upper respiratory effects at similar concentrations observed at 2 weeks (Coombs et al. 1992) compared to 13 weeks (Coombs et al. 1994) indicated only mild, respiratory tract effects were observed at the highest concentrations tested (i.e. 19 ppm for the 2-week study and 15.3 ppm for the 13-week study) and an increased severity of response was not observed except weight gain and food consumption were decreased in the subchronic study.

- There is only one rat study investigating the chronic effects of MET so a UF_D is needed. However, a UF_D of 3 was used instead of 10 because the MOA of MET indicates it is mainly a mild sensory and upper respiratory tract irritant at low concentrations and significant systemic absorption is not expected as shown by both the 2- and 13-week studies (Coombs et al. 1992; Coombs et al. 1994). The confidence in the database is low.

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

The resulting chronic ReV is 2.92 ppb. The chronic ReV was rounded to two significant figures at the end of all calculations resulting in a chronic ReV of 2.9 ppb (8.1 µg/m^3). The rounded chronic ReV was then multiplied by 0.3 to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient (HQ) of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 0.87 ppb (2.4 µg/m^3) (Table 6).

Table 6 Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Summary
Study	Coombs et al. 1994
Study population	Sprague Dawley male and female rats (10/sex/ group)
Study quality	High
Exposure methods	Exposures via inhalation at 0, 1, 4.9, and 15.3 ppm (analytical)
Critical effects	Extrathoracic respiratory tract effects
LOAEL	15.3 ppm
POD	4.9 ppm NOAEL
Exposure duration	6 h/day, 5 days/week for 13 weeks
POD_{ADJ}	0.875 ppm
POD_{HEC}	0.875 ppm (Category 1 vapor, $RGDR_{ET}$ = 1)
Total uncertainty factors (UFs)	300
Interspecies UF	3
Intraspecies UF	10
Subchronic to chronic UF	3
LOAEL UF	Not applicable
Incomplete Database UF	3
Database Quality	low
Chronic ReV [1 h] (HQ = 1)	**8.1 µg/m^3 (2.9 ppb)**
$^{chronic}ESL_{threshold(nc)}$ [1 h] (HQ = 0.3)	**2.4 µg/m^3 (0.87 ppb)**

4.2 Carcinogenic Potential

Chronic human or animal inhalation or oral studies indicating that MET has carcinogenic potential are not available, so a chronic carcinogenic value was not developed. Data from *in vitro* mutagenicity assays indicate that MET may be mutagenic.

4.2.1 *In vitro* Mutagenicity

MET tested positive in the Ames test using *Salmonella typhimurium* strains TA100 (Lutz et al. 1982; Eder et al. 1990; Neudecker et al. 1991; Eder and Deininger 2001) and TA104 (Mersch-Sundermann et al. 1994), but tested negative in *Salmonella typhimurium* strain TA98 (Kato et al. 1989). Using the TA110 strain, MET mutagenicity was shown to decrease following the addition of an active S-9 mix, suggesting a direct mechanism of action (Lutz et al. 1982; Eder et al. 1990;

Neudecker et al. 1991). This was further supported by Neudecker et al. (1991) who showed that inactivating the S-9 mix by heat or a chemical inhibitor did not affect the reduction in mutagenicity, indicating that MET does not rely on enzyme activity. Although several studies have shown negative results for MET in the SOS test (Benamira and Marnett 1992; Mersch-Sundermann et al. 1994; Eder et al. 1990, 1993, 1994), a more recent study determined that using ethanol rather than dimethyl sulfoxide as a solvent for MET gave positive results (Eder et al. 2002).

4.2.2 *In vivo* Mutagenicity

No *in vivo* mutagenicity studies were available for MET.

4.3. Welfare-Based Chronic ESL

No data were found regarding long-term vegetative effects.

4.4 Long-Term ESL

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

- $^{chronic}ESL_{threshold(nc)}$ = 2.4 µg/m^3 (0.87 ppb)
- Chronic ReV = 8.1 µg/m^3 (2.9 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 2.4 µg/m^3 (0.87 ppb) (Table 2). For the evaluation of ambient air monitoring data, the chronic ReV of 8.1 µg/m^3 (2.9 ppb) is used (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5 Chronic Observed Adverse Effect Level

The LOAEL value of 15.3 ppm determined in a rat 13-wk study (Coombs et al. 1994) (Table 6) was used as the POD for calculation of a chronic inhalation observed adverse effect level. No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to calculate a $LOAEL_{HEC}$:

The $LOAEL_{HEC}$ was calculated using the following equation:

$LOAEL_{HEC}$ = LOAEL x $RGDR_{ET}$ (Section 4.1.4.2.2)
= 15.3 ppm x 1
= 15.3 ppm
= 15 ppm or 15,000 ppb (rounded to two significant figures)

The $LOAEL_{HEC}$ determined from an animal study, where effects occurred in some animals, represents a concentration at which it is probable that similar effects could occur in some

individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. 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. The chronic inhalation observed adverse effect level of 42,000 µg/m^3 (15,000 ppb) is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the chronic inhalation observed adverse effect level of 15,000 ppb to the ReV of 2.9 ppb is a factor of approximately 5,200.

Chapter 5 References

5.1 References Cited in the Development Support Document

Acute Exposure Guideline Levels (AEGLs). 2008. Acute Exposure Guideline Levels for methacryaldehyde (CAS Reg. No. 78-85-3). Interim. Available at www.epa.gov/oppt/aegl.

Acute Exposure Guideline Levels (AEGLs). 2005. Acute Exposure Guideline Levels for acrolein (CAS Reg. No. 107-02-8). Interim. Available at www.epa.gov/oppt/aegl.

Atkinson, R and J Arey. 2003. (in Nøjgaard et al. 2005). Gas-phase troposheric chemistry of biogenic volatile organic compounds: A review. *Atmos Environ* 37, S 197-219.

Benamira M, LJ Marnett. 1992. (in AEGL 2008). The lipid peroxidation product 4-hydroxynonenal is a potent inducer of the SOS response. *Mutat Res* 293:1-10.

Carpenter CP, HF Smyth, UC Pozzani. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. *J Ind Hyg and Tox* 31: 343-346.

Coombs DW, TJ Kenny, CJ Hardy. 1992. MET (B. G. No. 108) 2-week repeat dose preliminary inhalation toxicity study in rats (Study report submitted ton the USEPA without data confidentiality restriction by B. G. Chemie). Huntingdon, Cambridgeshire, England.

Coombs DW, TJ Kenny, CJ Hardy. 1994. MET (B. G. No. 108) 13-week repeat dose preliminary inhalation toxicity study in rats (Study report submitted ton the USEPA without data confidentiality restriction by B. G. Chemie). Huntingdon, Cambridgeshire, England.

Eder E, C Hoffman, H Bastian, C Deininger, S Scheckenbach. 1990. Molecular mechanisms of DNA damage initiated by α,β-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity. *Env Health Per* 88:99-106.

Eder E, S Scheckenbach, C Deininger, C Hoffman. 1993. (in AEGL 2008). The possible role of

α,β-unsaturated carbonyl compounds in mutagenesis and carcinogenesis. *Toxicol Lett* 67:87-103.

Eder E, C Hoffman, C Deininger, S Scheckenbach. 1994. (in AEGL 2008). Risk assessment for mutagenic and carcinogenic activities of α,β-unsaturated carbonyl compounds by a screening strategy based on structure activity relationships. *Toxicol in vitro* 8:707-110.

Eder E, C Deininger. 2001. Mutagenicity of 2-alkylpropenals in *Salmonella typhimurium* strain TA 100: structural influences. *Env Mol Mutat* 37:324-328.

Eder E, C Deininger. 2002. The influence of solvents DMSO and ethanol on the genotoxicity of α,β-unsaturated aldehydes in the SOS chromotest. *Mutat Res* 516:81-89.

Hazardous Substances Data Bank (HSDB). 2002 update. United States National Library of Medicine, http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~mVE1q6:1, accessed June 27, 2008.

Hessamedin, A and WL Silver. 2000. (in AEGL 2008). Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. *Chem Senses* 25:61-66.

Kato FA, K Araki, K Nozaki, T Matsushima. 1989. (in AEGL 2008). Mutagenicity of aldehydes and diketones. *Mutat Res* 216:366.

Kessler A, R Halitschke, C Diezel, IT Baldwin. 2006. Priming of plant defense responses in nature by airborne signaling between *Artemisia tridentate* and *Nicotiana attenuate*. *Oecologia* 148: 280-292.

Larsen ST, GD Nielsen. 2000. Effects of MET on the respiratory tract in mice. *Toxicol Lett* 114: 197-202.

Lutz D, E Eder, T Neudecker, D Henschler. 1982. Structure-mutagenicity relationship in α,β-unsaturated carbonylic compounds and their corresponding allylic alcohols. *Mutat Res* 93:305-315.

Mersch-Sundermann V, U Schneider, G Klopman, HS Rosenkranz. 1994. (in AEGL 2008). SOS induction in *Escherichia coli* and *Salmonella* mutagenicity: a comparison using 330 compounds. *Mutagenesis* 9:205-224.

Nagata Y. 2003.Measurement of odor threshold by triangular odor bag method. Odor Measurement Review, Japan Ministry of the Environment 118-227.

National Institute for Occupational Safety and Health. Peer reviewed 1995. International Chemical Safety Cards: Methacrylaldehyde. Center for Disease Control,

http://www.cdc.gov/niosh/ipcsneng/neng1259.html, accessed June 27, 2008.

Nøjgaard, JK, KB Christensen and P Wolkoff. 2005. The effect of human eye blink frequency of exposure to limonene oxidation products and MET. *Toxicol Lett* 156: 241-51.

Neudecker T, E Eder, C Deininger, D Henschler. 1991. Mutagenicity of 2-methylacrolein, 2-ethylacrolein, and 2-propylacrolein in *Salmonella typhimurium*: A comparative study. *Mutat Res* 264:193-196.

Pedersen, T and K Sehested. 2001. Rate constants and activation energies for ozonolysis of isoprene MET and methyl-vinyl-ketone in aqueous solution: Significance to the in-cloud ozonation of isoprene. *Int J Chem Kinetics* 33: 182-90.

Texas Commission on Environmental Quality (TCEQ). 2012. TCEQ guidelines to develop toxicity factors (Revised RG-442). Office of the Executive Director. Austin, TX. Available from: http://www.tceq.texas.gov/publications/rg/rg-442.html

United Kingdom Compliance Programme. Department of Health & Social Security 1986 and subsequent revision, Department of Health Department of Health 1989.

United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development. Washington, D.C. EPA/600/8-90/066F.

United States Environmental Protection Agency (USEPA). 2012 Advances in inhalation gas dosimetry for derivation of a reference concentration (RfC) and use in risk assessment. Washington, D.C. EPA/600/R-12/044).

Wolkoff P, PA Clausen, CK Wilkins, GD Nielsen. 2000. Formation of strong airway irritants in terpene/ozone mixtures. *Indoor Air* 10:82-91.

5.2 Other Studies and Documents Reviewed by the Toxicology Division

Personius, TL, CL Wambolt, JR Stephens, RG Kelsey. 1984. Crude terpenoid influence on mule deer preference for sagebrush. *J Range Manage* 40:84-88.

Carvalho LR, PC Vasconcellos, W Mantovani, CS Pool, SO Pisani. 2005. Measurements of biogenic hydrocarbons and carbonyl compounds emitted by trees from temperate warm Atlantic rainforest, Brazil. *J Environ Monit* 7:493-9.