Development Support Document
Final September 4, 2015

Monoethanolamine

CAS Registry Number: 141-43-5

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AMCV	air monitoring comparison value
$^{\circ}C$	degrees Celsius
CNS	central nervous system
DSD	development support document
DAF	dose adjustment factor
ESL	effects screening level
$^{acute}ESL$	acute health-based effects screening level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based effects screening level
$^{acute}ESL_{veg}$	acute vegetation-based effects screening level
$^{chronice}ESL_{generic}$	chronic health-based effects screening level for chemicals not meeting minimum database requirements
$^{chronic}ESL_{threshold(c)}$	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
h	hour(s)
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury

Acronyms and Abbreviations	Definition
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram
LEL	lower explosive limit
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram
µg/m^3	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute(s)
MOA	mode of action
n	number
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
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

Acronyms and Abbreviations	Definition
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

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 monoethanolamine (MEA). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015a) 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 MEA's physical/chemical data.

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

Short-Term Values	Concentration	Notes
acute ReV (HQ = 1.0)	320 µg/m^3 (130 ppb) **Short-Term Health**	**Critical Effect:** Nasal irritation in dogs
$^{acute}ESL_{odor}$	- - -	Odor detection threshold is significantly above health-based value
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	23 µg/m^3 (9.3 ppb) **Long-Term Health**	Neurobehavioral effects (e.g., lethargy, slow movement) in rats
$^{chronic}ESL_{threshold(c)}$ $^{chronic}ESL_{nonthreshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Currently, the TCEQ does not monitor for MEA in the ambient air monitoring network.

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

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ (HQ = 0.3)	97 µg/m^3 (39 ppb)[a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Nasal irritation in dogs
$^{acute}ESL_{odor}$	---	Odor detection threshold is significantly above health-based value
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	7.0 µg/m^3 (2.8 ppb)[b] **Long-Term ESL for Air Permit Reviews**	Neurobehavioral (e.g., lethargy, slow movement) effects in rats
$^{chronic}ESL_{threshold(c)}$ $^{chronic}ESL_{nonthreshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 320 µg/m^3 (130 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 23 µg/m^3 (9.3 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
Chemical Structure		ChemIDPlus[a]
Molecular Weight	61.08	ACGIH (2001)
Molecular Formula	C_2H_7NO	ACGIH (2001)
Structural Formula	$HOC\text{-}CH_2\text{-}CH_2\text{-}NH_2$	ACGIH (2001)
Physical State	Liquid	ACGIH (2001)
Color	Colorless	ACGIH (2001)
Odor	Unpleasant ammonia-like	NIOSH (2007)
CAS Registry Number	141-43-5	ACGIH (2001)
Synonyms/Trade Names	Ethanolamine; 2-Aminoethanol; Dow™ monoethanolamine; Dow MEA GT Grades; MEA; Aminoethanolamine; 1-Amino-2-hydroxyethane; Beta-aminoethanol; Beta-aminoethyl alcohol; Beta-ethanolamine; Colamine; Ethanol, 2-amino-; Glycinol; 2-Hydroxyethanamine; Olamine	ACGIH (2001); Dow (2010)
Solubility in water @25°C	1E+06 mg/L	ChemIDPlus[a]
Log K_{ow}	1.98	ChemIDPlus[a]
pKa	9.499	ChemIDPlus[a]
Vapor Pressure @25°C	0.404 mm Hg	ChemIDPlus[a]
Vapor Density (air = 1)	2.1 at 0°C	ACGIH (2001)
Density (water = 1)	1.012 g/mL at 25°C	Chemical Book[b]
Melting Point	10.3°C	ACGIH (2001)
Boiling Point	170.8°C	ACGIH (2001)
Lower Explosive Limit	3.0%	NIOSH (2007)
Conversion Factors	1 ppm = 2.50 mg/m^3 1 mg/m^3 = 0.401 ppm	ACGIH (2001)

[a] Data accessed July 17, 2014

[b] Accessed December 12, 2014

Chapter 2 Major Sources or Uses

MEA is an amino alcohol that is permitted in articles intended for use in the production, processing, and packaging of food. MEA is also a softening agent for hides, a dispersing agent for agricultural chemicals, and is used in polishes, hair waving solutions, and in the synthesis of surface-active agents (Melnick and Tomazewski 1990; ACGIH 2001; Lag et al. 2009). MEA undergoes reactions characteristic of primary amines and alcohols (Melnick and Tomazewski 1990).

Industrially, MEA is used in the removal of carbon dioxide and hydrogen sulfide from natural gas and other gases. Also, MEA is often used industrially as a minor constituent in combination with varying concentrations/percentages of other amino alcohol mixtures, including diethanolamine (DEA) and triethanolamine (TEA) to modify the properties of compounds. Biologically, MEA is a normal intermediate in human and animal metabolism, having a role in the formation of phospholipids and choline. A certain amount of free MEA is also excreted in the urine of unexposed humans (Luck and Wilcox 1953; Weeks et al. 1960; NRC 2007; Scientific Basis for Swedish Occupational Standards (SBSOS) 2013).

Currently, MEA does not appear on the list of hazardous air pollutants, thus it is not measured by the USEPA's ambient air quality monitoring program that is implemented by state and local agencies, including the TCEQ, for non-criteria pollutants.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV

MEA has been classified by the ACGIH (2008) as an irritant to eyes and skin. Additionally, short-term exposure to significantly elevated inhaled doses for a sufficient duration can lead to central nervous system (CNS) effects, nasal irritation, or pulmonary edema (Weeks et al. 1960; Kamijo et al. 2004).

3.1.1 Physical/Chemical Properties

MEA is a colorless liquid with an ammonia-like odor (ACGIH 2001). MEA is also a strong base that is soluble in water, alcohol, and petroleum distillates (Liebert 1983). MEA along with other amino alcohols (i.e., DEA and TEA) can be local irritants in concentrated solutions. Due to the photochemical reactivity of the hydroxyl group, the half-life of MEA in the atmosphere is approximately 27 hours (h) (Canada 2010). Also, in view of MEA's low vapor pressure, significant exposure by inhalation is improbable under normal (i.e., non-industrial/unconcentrated) circumstances (Savonius et al. 1994). The chemical and physical properties of MEA are summarized in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

This section is based on a review of current literature as well as background documents (e.g., ACGIH 2001). Acute inhalation toxicity information for MEA is sparse for both animals and humans. Although human data are preferred (TCEQ 2015a), only qualitative information regarding the acute toxicity of MEA (e.g., decreased peak expiratory flow (PEF), occupational asthma) is available from human studies. Thus, available human data are very limited and unsuitable for quantitative dose-response assessment. A couple of these qualitative studies are briefly highlighted here:

- Savonius et al. (1994) describes results from lung function and provocation tests of three patients with occupational asthma reportedly caused by ethanolamines (MEA, DEA, and TEA). Two male patients in this study included a metal worker and a "turner" worker that were challenged with heated cutting fluids as well as fumes from turning and cooling fluids, respectively. These fluids contained 14% to pure TEA and resulted in a maximum drop in peak expiratory flow (PEF) of 21%. The third patient, a female "cleaner," experienced a 24% maximum drop in PEF and a 27% decrease in forced expiration volume in one second (FEV_1) after being challenged with a detergent containing 8% MEA in hot water. In addition, the female patient developed a low-grade fever 7 h after exposure. Two hyper-reactive control patients did not develop significant PEF decrements. Overall, substantial exposure to heated vapors of ethanolamines may cause decreases in PEF/FEV_1.
- Suuronen et al. (2007) analyzed 1992-2001 data on 1,027 occupational diseases, the most prevalent were hearing loss (31%), skin ailments (i.e., contact, irritant, and allergic dermatitis, acne) (27%), and strain injuries (26%). Asbestos-related diseases accounted for 9%, other diseases accounted for 4%, and allergic respiratory diseases (e.g., asthma and rhinitis) accounted for 3% of the occupational diseases mostly diagnosed in male machinists related to metalworking fluids (MWFs). MWFs are a mixture of base oils and auxiliary substances such as emulsifiers (e.g., ethanolamines), antimicrobial agents, corrosion inhibitors, extreme pressure additives, etc. In general, the incidence of occupational disease was 5.9 cases per 1000 person-years among machinists and 2.7 cases per 1000 person-years in the general workforce. The study reported a total of 279 cases of occupational skin diseases (OSDs) and a total of 34 cases of allergic respiratory diseases (ARD) in machinists. The OSDs were comprised of allergic contact dermatitis (39%), irritant contact dermatitis (53%), contact urticarial or protein contact dermatitis, occupational acne, paronychia, skin infections, and others (i.e., unspecified skin diseases). The most commonly noted causes of allergic contact dermatitis were attributed to formaldehyde, ethanolamines (MEA, DEA, and TEA), colophony (a.k.a. rosin), and metals. Of the 34 ARDs, the most common diagnosis was occupational asthma (29), with four cases being associated with allergic rhinitis, and one case of allergic alveolitis.

Suuronen et al. also reported that the primary causative agents in these asthma cases were metals and synthetic resins and one asthma case was reported to be caused by DEA specifically. These asthma cases were confirmed by specific challenge tests in 12 cases and by a workplace challenge in one case. The FEV_1 decreases varied between 16 and 37% and the PEF decreases varied between 17 and 30%. Overall, and along with other constituents, ethanolamines were qualitatively identified by Suuronen et al. as potentially causative agents for OSDs and ARDs.

3.1.2.2 Animal Studies

Weeks et al. (1960) is the most comprehensive inhalation animal study conducted to date for MEA (e.g., ACGIH 2001 selected the lowest dose of 5 ppm as the basis for its threshold limit value recommendation). Other inhalation animal studies such as Treon et al. (1954) and Dow (2013, unpublished) which assessed mortality and Rohr et al. (2013) which assessed cytokine expression and oxidative stress provide less information for derivation of an acute ReV. They are included here only to provide qualitative insight into the overall acute inhalation toxicity of MEA.

- Treon et al. (1954) conducted an inhalation toxicity study for MEA using rats, guinea pigs, mice, rabbits, rats, cats, and dogs. Animals were exposed to various chamber concentrations of MEA (≈ 50 to 1,200 ppm) for various durations (i.e., 0.25, 1, 1.5, 3.5,7, 21, and 35 h; 7 h/day (d) for 2,3,4,5, and 25 d) to assess mortality. For this mortality endpoint, the study qualitatively established guinea pigs as the most sensitive rodent (experience more deaths at lower exposure concentrations and shorter exposure durations).

- Dow (2013), an unpublished acute inhalation lethality study, reported that a calculated concentration of approximately 3,068 ppm (8,420 mg/m^3) produced lethality in 50% (LC_{50}) of the tested female rats. F344/DuCrl rats in groups of 2 animals/sex were exposed to calculated MEA concentrations of 2,536 ppm (6,340 mg/m^3) and 4,468 ppm (11,170 mg/m^3) in inhalation chambers for different durations (e.g., 15, 30, 60, 120, and 240 minutes (min)). Death occurred at the highest concentration only at the 120 and 240 min exposure durations.

- Rohr et al. (2013) conducted a mouse acute inhalation study of three different amines (MEA, methlydiethanolamine (MDEA), and piperazine (PIP)) and their respective degradation products. This study was aimed at investigating the pulmonary inflammatory potential of the inhaled amines and degradants. Cytokine expression and oxidative stress were measured in mouse lung tissue after an exposure to 10-25 ppm MEA for 6 h/d for 7 d. None of the amines, including MEA, produced a statistically significant impact on cytokine expression. MEA was the only amine that produced a statistically significant decrease in oxidative stress as determined by TBARS levels in C57bl/6N mouse lung. Rohr et al. reported that initial studies with MEA at 10 ppm

resulted in no inflammatory response. Additionally, in an email communication (10/21/2014), co-author Dr. Jacob McDonald (a researcher at the Lovelace Respiratory Research Institute in Albuquerque, New Mexico) noted that there were some behavioral observations (i.e., agitation in mice) at 25 ppm that could be indicative of nasal irritation. This observation was not reported in Rohr et al., although it is noted that this observation is consistent with the "immediate" irritation reported in dogs at 26 ppm in Weeks et al. Overall, Rohr et al. results suggest that inhalation exposure to amines at high concentrations poses minimal potential for lung inflammation under acute exposure conditions, yet suggest potential for nasal irritation at 25 ppm. Even though this study is the latest published toxicity information on MEA it was not used as the key study because Weeks et al. (1960) provided more comprehensive and quantitative animal inhalation toxicity information.

Additional information in NRC (2007), ACGIH (2001), and Melnick and Tomazewski (1990) summarizes other acute and subacute animal studies that involve several species of laboratory animals (e.g., dogs, rats, mice, rabbits, and guinea pigs) exposed to MEA by additional routes (i.e., intraperitoneal, oral, and dermal). For purposes of deriving inhalation toxicity factors, Weeks et al. (1960) is the most comprehensive and suitable inhalation animal study conducted to date.

3.1.2.2.1 Key Study (Weeks et al. 1960)

Weeks et al. (1960) was a continuous exposure study that included dogs, guinea pigs, and rats and reported concentration- and duration-dependent skin, nasal, and lung irritation and lethargy as the dominant adverse effects. Three mature male beagle hounds per exposure group, six-week old male guinea pigs (Hartley strain, n = 22 or 30), and eight-week old female rats (CW Laboratories, n = 45) per exposure group were exposed to analytical intermediate (12-26 ppm) and high (66-102 ppm) concentrations of MEA for 24 to 90 d. For the low analytical concentrations of MEA (5-6 ppm), 20 young (4-6 weeks old) male and female rats and three mature male beagle hounds were exposed for 40 d and 60 d, respectively.

Dogs tolerated a much higher concentration of MEA than rodents, with two dogs surviving 30-d exposure at the highest doses (66-102 ppm). At their respective highest dose, 83% of the rats and 75% of the guinea pigs died after 28- and 24-d exposure, respectively. The two surviving dogs developed lung irritation (i.e., moist rales) by the middle of the second week, which was associated with a low grade fever (103-104°F) that ran a course of about two weeks. Depressed, lethargic, and apathetic states were noted in all animals that survived the high dose (66-102 ppm). Other common effects like skin lesions on ground contact points (feet, nose, lips, and chin) and skin points of tension (around extensor surface of larger joints) showed dark eschars (i.e., dry scabs that form on burned skin) which covered ulcerated skin beneath. These dermal-related effects may be associated with the animals constantly in contact with MEA condensate as it accumulated on the walls and floors of the exposure chambers throughout the experiments.

All animals survived their respective intermediate concentrations (12-26 ppm) of MEA vapor for 90 d. Signs and symptoms were similar to those seen at the high concentrations, but not so severe. Dogs exposed to 26 ppm MEA showed “immediate” signs of restlessness and discomfort, indicated by nose-pawing, muzzle-licking, and shallow-rapid respiration (while the specific duration is not stated, as irritation is primarily concentration dependent, it was assumed the “immediate” irritant effects reported would also occur at a 1-h duration). Throughout the experiment these dogs were more irritable than controls, and after a few days of exposure were less alert and bordered variably on lethargy. Slight tremors of rear leg muscles were also noted. Also, skin at floor contact points on the chest and scrotum of the dogs became irritated, which was relieved by ointment.

Dogs exposed to 12 ppm of MEA for 90 d did not show immediate behavioral changes. No significant weight changes occurred nor did physical examinations reveal any changes. However, after several days their skin became irritated and soothing ointment was applied, which relieved the condition and the skin showed no further signs of irritation. Concurrently, lethargy or depression appeared and lasted about three weeks before their behavior returned to normal. Rodents exposed to 12-15 ppm of MEA became less active than the controls after about 3 d, and showed definite lethargy after about 10 d, which lasted throughout the balance of the exposure. In addition to hair loss, rodents showed an approximate 10% reduction in weight gain and approximately a 40% increase in water consumption.

For the low exposure group, young (4-5 weeks old) male and female rats and mature male beagle dogs were exposed to 5 and 6 ppm of MEA for 40 d and 60 d, respectively. All animals survived exposure to these low concentrations. Neurobehavioral changes in animals were noted after 2-3 weeks of continuous exposure at these concentrations. In dogs, a slight decrease in alertness and activity was noted. Two of the three exposed dogs also showed slight weight loss concurrently. No changes from normal were observed in pulse, temperature, and heart and lung sounds. Skin irritation and hair loss occurred on chest-floor contact areas, and the scrotum became bare and spotted with small scattered black eschars. All rats exposed to 5 ppm showed pelt discoloration after 12 d and transitory hair loss on the head and back after three weeks, which was more pronounced in the females. Additionally, some slowness in movement developed in rats after three weeks of exposure which lasted throughout the 40-d exposure duration.

Based on the results of this study, 12 ppm was selected as the acute NOAEL for nasal irritation symptoms (e.g., nose-pawing, shallow breathing) in dogs. The associated LOAEL of 26 ppm is consistent with the agitation of mice at 25 ppm (perhaps due to nasal irritation) reported in a personal communication by a co-author of the Rohr et al. (2013) study. Concentrations in the 5-6 ppm range were not selected because the neurobehavioral changes associated with these concentrations occurred in test animals after 2-3 weeks of continuous exposure. Thus, the associated LOAEL of 26 ppm demonstrated in Weeks et al. produced a more immediate effect and is more relevant for the development of an acute toxicity value.

3.1.2.2.2 Consideration of Developmental/Reproductive Effects

Developmental effects are considered for derivation of the acute ReV and ESL (TCEQ 2015a). No robust inhalation exposure developmental studies were located for MEA in humans or laboratory animals. However, Weeks et al. (1960) did report that spermatogenesis appeared decreased in guinea pigs at the highest concentration (75 ppm) where 75% of the animals died. In regard to other routes of exposure, oral animal MEA developmental and reproductive studies were evaluated in the recent SBSOS (2013) consensus report and in Hellwig and Liberacki (1997), which both reported no significant reproductive effects in rabbits and/or rats at oral doses ranging from 40-500 mg/kg-d for days 6-15 of gestation. A rat developmental and reproductive NOAEL of 450 mg/kg-d was identified by Hellwig and Liberacki (1997) which corresponds to an equivalent air concentration of approximately 160 ppm. This equivalent air concentration NOAEL is significantly higher than the LOAEL of 26 ppm for nasal irritation from the key study (Weeks et al. 1960) and more than 10 times higher than the associated NOAEL of 12 ppm. Based on the above discussion, protecting against the critical effects observed in Weeks et al. (1960) is expected to also be protective of potential developmental and reproductive effects.

3.1.2.2.2.3 Consideration of Sensitizer Effects

MEA, DEA, and TEA are three amino alcohols that have a local irritant effect in concentrated solutions and have been associated with sensitization (i.e., occupational contact dermatitis and occupationally induced asthma) in cleaners and metal workers (Savonius 1994; Suuronen 2007; Gerster 2014). Lessmann et al. (2009) pointed out that MEA in water-based metalworking fluids and the regular, even daily exposure to these fluids is regarded as a cause of occupational sensitization in metal workers. However, Lessmann et al. dually noted that the wet work or chemical irritation by solvents or the alkaline cutting fluids, and possibly mechanical irritation, seems to be important cofactors in contributing to sensitization in these metal workers. Overall, MEA alone does not cause allergic sensitization in standard animal tests, and human patch testing has not shown MEA to be a significant sensitizer (Lessmann 2009; Dow 2010).

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

MEA is an amino alcohol in which one ethanol group is attached to an amino group; therefore, MEA has properties of both amines and alcohols. As an amine, it is alkaline with a pKa of 9.5, and as an alcohol it is hydrophilic (Kamijo et al. 2004). Thus, the MOA for the critical MEA-induced nasal irritation effects may be related to a combination of both properties and the fact that MEA may be corrosive (e.g., pH $\geq$ 11.5). Furthermore, parent chemical concentration is the only dose metric available for the key study. Therefore, the exposure concentration of the parent chemical was used as the dose metric.

3.1.4 POD for the Key Studies and Critical Effect

The acute NOAEL of 12 ppm for the critical effects of nasal irritation symptoms in dogs (Weeks et al. 1960) is used as the POD to derive an acute ReV for MEA.

3.1.5 Dosimetric Adjustments

3.1.5.1 Exposure Duration Adjustments

The POD (NOAEL of 12 ppm) is based on the lack of nasal irritation symptoms in dogs in the Weeks et al. (1960) study. Because irritation is primarily a concentration-dependent effect, a duration adjustment is not applied (TCEQ 2015a).

3.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The acute critical effect, nasal irritation, is a point-of-entry effect. MEA was therefore considered a Category 1 vapor (TCEQ 2015a). Category 1 gases/vapors that cause local effects are typically highly reactive or water soluble chemicals. A default animal-to-human dosimetric adjustment factor (DAF) of 1 is applied when the critical effect is in the extrathoracic (ET) region (TCEQ 2015a). Therefore, the NOAEL-based POD_{HEC} for 1-h exposure is 12 ppm.

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

The POD_{HEC} of 12 ppm MEA from Weeks et al. (1960) based on nasal irritation effects was selected to derive the acute ReV and ^{acute}ESL for MEA. Consistent with the limited toxicity information available, the exact MOA for MEA's critical effects is not fully elucidated. The default approach for threshold effects is to determine a POD and apply appropriate UFs to derive the acute ReV (TCEQ 2015a).

A total UF of 90 was calculated for application to the POD_{HEC} of 12 ppm MEA to derive the acute ReV: an intrahuman UF_H of 10; a UF_A of 3 for extrapolation from animals to humans; and a UF_D of 3 to account for deficiencies in the medium-high database. The following is more specific information concerning the rational for the UF values:

- A full UF_H of 10 was considered appropriate to account for potential intrahuman variability since, although ethanolamines (i.e., MEA, DEA, and TEA) have been implicated in occupational asthma, information on potentially sensitive subpopulations sufficient to inform selection of another value is lacking.
- An UF_A of 3 was applied for interspecies variability because, while a dosimetric adjustment was conducted, potential interspecies toxicodynamic differences were not accounted for.
- An UF_D of 3 was applied for uncertainty associated with an incomplete database due to the lack of a more robust acute inhalation dataset. A full UF_D of 10 was not used because the key study did evaluate toxicity endpoints in multiple animal species and some information is available on the potential for developmental/reproductive effects. The quality of the key study is considered medium, and confidence for the database is considered medium-high (e.g., the inhalation study for acute ReV derivation used multiple animal species).

Acute ReV = POD_{HEC} / (UF_H x UF_A x UF_D)
= 12 ppm / (10 x 3 x 3)
= 0.133 ppm
= 130 ppb (320 µg/m^3) (rounded to two significant figures)

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

In deriving the acute ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded acute ReV was then used to calculate the acute ESL, and the ESL subsequently rounded. The acute ReV of 130 ppb (320 µg/m^3) was multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations to calculate the ^{acute}ESL of 39 ppb (97 µg/m^3) for MEA (Table 4).

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

Parameter	**Summary**
Study	Weeks et al. 1960
Study Population	Male beagle dogs
Study Quality	Medium
Exposure Method	Continuous exposure via inhalation at 0, 5, 12, and 66 ppm (target concentrations)
Critical Effects	Nasal irritation symptoms
POD	12 ppm (NOAEL)
Exposure Duration	90 d although nasal irritation symptoms occurred with acute exposure
POD_{HEC}	12 ppm (DAF = 1)
Total UF	90
Interspecies UF	10
Intraspecies UF	3
Incomplete Database UF	3
Database Quality	Medium-high
Acute ReV [1 h] (HQ = 1)	**320 µg/m^3 (130 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**97 µg/m^3 (39 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

MEA has a characteristic ammonia-like odor. An odor detection threshold of 2.6 ppm, with a 95% confidence interval of 2 to 3.3 ppm, was reported by Weeks et al. (1960) using 12 human subjects. The subjects detected the presence of the vapors by means of sensation rather than odor and reported a describable odor at around 25 ppm. ACGIH (2001) and AIHA (2013) also cite Weeks et al. (1960) as the source for their odor threshold of 3 to 24 ppm. Please note that the acute health-based ReV (130 ppb) and ^{acute}ESL (39 ppb) are well below the reported odor detection threshold in Weeks et al. (1960), ACGIH (2001), and AIHA (2013) and are expected to prevent odorous conditions. Therefore, in accordance with TCEQ (2015b), no odor threshold value will be developed.

3.2.2 Vegetation Effects

No information was found in the literature to indicate that special consideration should be given to possible vegetation effects from MEA.

3.3 Short-Term ESL

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

- Acute ReV = 320 µg/m^3 (130 ppb)
- ^{acute}ESL = 97 µg/m^3 (39 ppb)

Currently, there are no ambient air monitoring data for MEA in Texas or anywhere in the United States. However, the acute ReV of 320 µg/m^3 (130 ppb) would be used for the evaluation of any ambient air monitoring data, if monitored in the future (Table 1). The ^{acute}ESL for air permit reviews is 97 µg/m^3 (39 ppb) (Table 2). The ^{acute}ESL would not be used to evaluate any future ambient air monitoring data.

3.4 Acute Inhalation Observed Adverse Effect Level

The study by Weeks et al. (1960) had an acute LOAEL of 26 ppm (Table 4) for immediate nasal irritation in dogs. The TCEQ notes that the basis for development of inhalation observed adverse effect levels for MEA is limited to available data, and also notes that future studies could possibly identify a lower POD for this purpose. As the critical effect is in the ET region, the animal-to-human DAF is 1 (TCEQ 2015a), and the POD_{HEC} is also 26 ppm. This POD_{HEC} determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The estimated acute inhalation observed adverse effect level of 26 ppm MEA is provided for informational purposes only (TCEQ 2015a).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

No long-term inhalation human studies were located in the available literature for the chronic evaluation of MEA. However, in regard to laboratory animals, Weeks et al. (1960) included subchronic exposure of dogs, guinea pigs, and rats. This study reported concentration- and duration-dependent skin and respiratory irritation and lethargy as the dominant adverse effects due to continuous, intermediate (i.e., subacute to subchronic) exposure.

4.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.2 Key/Relevant Studies

4.1.2.1 Human Studies

According to SBSOS (2013) as well as the TCEQ scientific literature review, there are no human data from which to identify a critical effect for occupational exposure to MEA or derive a chronic inhalation value. Thus, the TCEQ based the development of chronic toxicity factors on the most reliable available animal inhalation study, Weeks et. al. (1960).

4.1.2.2 Animal Studies

4.1.2.2.1 Key Study (Weeks et al. 1960)

In the subchronic exposure portion of this animal inhalation study, all animals survived their respective intermediate concentrations (12-26 ppm) of MEA vapor for 90 d. Signs and symptoms were similar to those seen at the high concentrations (66, 75, and 102 ppm) for 24 d or 30 d, but not as severe. Dogs exposed to 12 ppm of MEA for 90 d did not show immediate nasal irritation/behavioral changes. At 12-26 ppm no significant weight changes occurred nor did physical/gross and microscopic examinations reveal any exposure-related changes. After several days their skin became irritated and soothing ointment was applied which relieved the condition and the skin showed no further signs of irritation. Concurrently, lethargy or depression appeared and lasted about three weeks before dog behavior returned to normal. Rodents (e.g., rats, guinea pigs) exposed to 12-15 ppm of MEA for 90 d became less active than the controls after about three days, and showed definite lethargy after about 10 d, which lasted throughout the balance of the exposure. In addition to hair loss, rodents showed an approximate 10% reduction in weight gain and approximately a 40% increase in water consumption.

Also, groups of young (4-5 weeks old) male and female rats and male beagle dogs were exposed to 5 and 6 ppm of MEA for 40 d and 60 d, respectively. Neurobehavioral changes in animals were noted after 2-3 weeks of continuous exposure at these concentrations. In dogs, a slight decrease in alertness and activity was noted. Two of the three exposed dogs also showed slight

weight loss concurrently. No changes from normal were observed in pulse, temperature, and heart and lung sounds. Additionally, some slowness in movement developed in rats after three weeks of exposure which lasted throughout the 40-d exposure duration. Weeks et al. describe these effects as minimal.

Thus, the 40-d rat and 60-d dog exposures at 5 and 6 ppm, respectively, resulted in some minimal neurobehavioral changes after 2-3 weeks. These effects lasted throughout the remainder of the balance of the exposure duration. Rodents (i.e., rats, guinea pigs) exposed to 12-15 ppm of MEA for 90 d also became less active and showed lethargy, which lasted throughout the balance of the exposure. The TCEQ selected 5 ppm as the lowest subchronic LOAEL for development of the chronic ReV based on neurobehavioral effects (e.g., lethargy, slow movement) in rats described by study authors as minimal.

4.1.2.3 Consideration of Developmental/Reproductive Effects

Developmental effects are considered for derivation of the chronic ReV and ESL (TCEQ 2015a). As stated before in the acute section, no robust inhalation exposure developmental studies were located for MEA in humans or laboratory animals (see Section 3.1.2.2.2). In regard to other routes of exposure, oral animal MEA developmental and reproductive studies were evaluated in the recent SBSOS (2013) consensus report and in Hellwig and Liberacki (1997). Both reported no significant reproductive effects on rabbits and/or rats at oral doses ranging from 40-500 mg/kg-d for days 6-15 of gestation. A rat developmental and reproductive NOAEL of 450 mg/kg-d was identified by Hellwig and Liberacki (1997) which corresponds to an equivalent air concentration of approximately 160 ppm. This equivalent air concentration is significantly higher than the 40-d rat and 60-d dog LOAELs of 5 and 6 ppm, respectively, identified in Weeks et al. (1960). Based on this information, protecting against the critical subchronic effects observed in the Weeks et al. (1960) is expected to also be protective of potential developmental and reproductive effects.

4.1.3 MOA Analysis and Dose Metric

The MOA for the critical MEA-induced neurobehavioral/CNS effects after subchronic exposure has not been elucidated. Furthermore, parent chemical concentration is the only dose metric available for the key study. Thus, exposure concentration of the parent chemical will be used as the dose metric.

4.1.4 POD for the Key Study and Critical Effect

Based on the key study presented above (Weeks et al. 1960), the TCEQ identifies 5 ppm (12.5 mg/m^3) as the minimal LOAEL and subchronic POD based on rat neurobehavioral effects.

4.1.5 Dosimetric Adjustments

4.1.5.1 Exposure Duration Adjustments

The 40-d exposure duration used in the key study was a subchronic, continuous exposure protocol. Therefore, no duration adjustment to continuous exposure is needed.

4.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

The critical effects (neurobehavioral effects) identified in the key study (Weeks et al. 1960) are systemic in nature. MEA was therefore considered a Category 3 vapor (TCEQ 2015a). For Category 3 vapors, the default dosimetric adjustment from an animal concentration to a POD_{HEC} is conducted using the following equation:

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

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

No measured values were found in the literature for the blood/air partition coefficients in humans ($(H_{b/g})_H$) and animals ($(H_{b/g})_A$) for MEA. Therefore, the default value of one (1) was used as a ratio of the animal-to-human partition coefficients. The resulting POD_{HEC} based on the POD of 5 ppm in the Weeks et al. (1960) study is therefore 5 ppm.

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 5 \text{ ppm} \times 1 = 5 \text{ ppm}$$

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

The subchronic POD_{HEC} of 5 ppm MEA based on the critical effects identified from Weeks et al. (1960) (e.g., neurobehavioral effects of slowness of movement/lethargy due to CNS depression) was used to derive the chronic ReV and ^{chronic}ESL for MEA. Weeks et al. also described this "narcotic" effect as the one with the "greatest danger" as it pertains to the potential for continuous human exposure. Consistent with the limited available toxicity information, the exact MOA for these MEA-induced critical effects is not fully elucidated. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the chronic ReV (i.e., assume a threshold MOA) (TCEQ 2015a).

A total UF of 540 was applied to the POD_{HEC} of 5 ppm MEA to derive the chronic ReV: 10 for UF_H, 3 for UF_L, 3 for UF_A, 2 for UF_{Sub}, and 3 for UF_D (see below). The following is more specific information concerning the rational for the UF values:

- An UF_H of 10 was considered appropriate to account for potential intrahuman variability. Although ethanolamines (i.e., MEA, DEA, and TEA) have been implicated in

occupational asthma, information on potentially sensitive subpopulations sufficient to inform selection of another value is lacking.

- An UF_L of 3 for extrapolation from a LOAEL to a NOAEL as the study authors describe the effects at 5 ppm as minimal.
- An UF_A of 3 for interspecies variability because a dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences.
- An UF_{Sub} of 2 was considered appropriate to account for use of a subchronic study due to reduced concern about bioaccumulation (i.e., log K_{ow} is well below 4). More importantly, there is reduced concern about chronic study effects differing significantly from subchronic effects because the continuous nature of the exposure for this 40- to 90-d study makes it similar from a total exposure perspective to a chronic study employing the usual 6 h/d exposure regimen (e.g., 40-d exposure for 24 h/d = 960 h = 160-d chronic study using a typical exposure regimen of 6 h/d).
- An UF_D of 3 for uncertainty associated with an incomplete database due to the lack of a more robust inhalation dataset. A full UF_D of 10 was not used because the key study did evaluate toxicity endpoints in multiple animal species using a continuous exposure regime and some information is available on the potential for developmental/ reproductive effects. The quality of the key study is considered medium, and confidence for the database is considered medium-high (e.g., the inhalation study used for chronic ReV derivation used multiple animal species).

Chronic ReV $= POD_{HEC} / (UF_H \times UF_L \times UF_A \times UF_{Sub} \times UF_D)$
$= 5 \text{ ppm} / (10 \times 3 \times 3 \times 2 \times 3)$
$= 5 \text{ ppm} / 540$
$= 0.00926 \text{ ppm}$
$= 9.3 \text{ ppb } (23 \text{ µg/m}^3)$ (rounded to two significant figures)

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

In deriving the chronic ReV, no numbers were rounded between equations until the ReV was calculated. The chronic ReV was rounded to two significant figures, resulting in a value of 9.3 ppb (23 µg/m^3), and then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 2.8 ppb (7.0 µg/m^3) (Table 5).

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

Parameter	**Summary**
Study	Weeks et al. 1960
Study Population	Male and female rats from CW Laboratories colonies
Study Quality	Medium
Exposure Method	Continuous exposure via inhalation at 0, 5 ppm (40 d), 6 ppm (60 d), 12, 15, 26 ppm (90 d)
Critical Effects	Neurobehavioral effects/CNS depression
POD (LOAEL)	5 ppm
Exposure Duration	40 d
POD_{HEC} (DAF = 1)	5 ppm
Total UF	540
Intraspecies UF	10
LOAEL UF	3
Interspecies UF	3
Subchronic to chronic UF	2
Database UF	3
Database Quality	Medium - high
Chronic ReV (HQ = 1)	**23 µg/m^3 (9.3 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**7.0 µg/m^3 (2.8 ppb)**

4.2 Carcinogenic and Mutagenic Potential

In the scientific literature, there are no studies available to assess the carcinogenicity of MEA. Relatedly, MEA was not found to be mutagenic in various *in vitro* tests on bacteria (*i.e., Salmonella typhimurium, Escherichia coli*) as summarized in SBSOS (2013). Also, mitotic gene conversions were not induced in yeast fungus tests with or without activation, no structural chromosome damage was present in rat liver cells, and no morphological cell transformations were observed in hamster embryo cells seen in other *in vitro* experiments (SBSOS 2013). Therefore, in accordance with the TCEQ (2015a) guidelines, the TCEQ classifies the carcinogenic weight of evidence (WOE) for MEA as – "*Data Are Inadequate for an Assessment of Human Carcinogenic Potential."* Thus, a carcinogenic dose-response assessment cannot be performed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation effects.

4.4 Long-term ESL

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

- Chronic ReV = 23 µg/m^3 (9.3 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 7.0 µg/m^3 (2.8 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 7.0 µg/m^3 (2.8 ppb) (Table 2). Although TCEQ does not currently monitor for MEA, the chronic ReV of 23 µg/m^3 (9.3 ppb) could be used for the evaluation of any ambient air monitoring data in the future (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) would not be used to evaluate ambient air monitoring data.

4.5 Subchronic Inhalation Observed Adverse Effect Level

The key study for derivation of the chronic ReV included results from a 40-d subchronic animal study portion, which will be used to derive a subchronic (i.e., not chronic) inhalation observed adverse effect level. 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 study by Weeks et al. (1960) had a subchronic LOAEL of 5 ppm (Table 5) for neurobehavioral effects/CNS depression in rats. This laboratory animal LOAEL was used as the animal subchronic inhalation observed adverse effect level for extrapolation to humans for this endpoint. No duration adjustment was made (TCEQ 2015a), and the corresponding POD_{HEC} is 5 ppm.

This POD_{HEC} determined from an animal study represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration reported to be associated with these effects in the study (i.e., beginning after 2-3 weeks of exposure), or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The estimated subchronic inhalation observed adverse effect level of 5 ppm MEA (40 d) is provided for informational purposes only (TCEQ 2015a).

Chapter 5. References

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