# Diethanolamine

## CAS Registry Number: 111-42-2

# Triethanolamine

## CAS Registry Number: 102-71-6

Prepared by
Darrell D. McCant, M.P.H.
Jessica L. Myers, Ph.D.
Joseph T. Haney, M.S.
Toxicology Division

## Development Support Document
## Final, June 28, 2018

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

# DSD History

| Effective Date | Reason |
|---|---|
| July 16, 2013 | Public request for toxicity information |
| March 8, 2018 | DSD proposed for public comment |
| June 28, 2018 | DSD posted as final |

# TABLE OF CONTENTS

# LIST OF TABLES



# LIST OF FIGURES

# Acronyms and Abbreviations

| Acronyms and Abbreviations | Definition |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AEGL | Acute Exposure Guideline Levels |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| $^{\circ}$C | degrees Celsius |
| BMR | benchmark response |
| bw | body weight |
| DSD | development support document |
| 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 |
| 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 |

| Acronyms and Abbreviations | Definition |
|---|---|
| HSDB | Hazardous Substance Data Base |
| IARC | International Agency for Research on Cancer |
| IOAEL | inhalation observed adverse effect level |
| $^{acute}$IOAEL | acute inhalation observed adverse effect level |
| $^{subacute}$IOAEL | subacute inhalation observed adverse effect level |
| $^{chronic}$IOAEL$_{(nc)}$ | chronic inhalation observed adverse effect level (noncancer effects) |
| $^{chronic}$IOAEL$_{(c)}$ | chronic inhalation observed adverse effect level (cancer effects) |
| IPCS | International Programme on Chemical Society |
| IRIS | USEPA Integrated Risk Information System |
| kg | kilogram |
| $K_{ow}$ | n-octanol-water partition coefficient |
| $LC_{50}$ | concentration causing lethality in 50% of test animals |
| $LD_{50}$ | dose causing lethality in 50% of test animals |
| LOAEL | lowest-observed-adverse-effect-level |
| LTD | limited toxicity data |
| mm Hg | A millimeter of mercury; approximately 1 torr, or 1/760 of standard atmospheric pressure |
| MW | molecular weight |
| MWFs | metal working fluids |
| µg | microgram |
| µg/m$^3$ | micrograms per cubic meter of air |
| mg | milligrams |
| mg/m$^3$ | milligrams per cubic meter of air |
| min | minute |
| MOA | mode of action |
| n | number |
| NOAEL | no-observed-adverse-effect-level |
| NOEL | no-observed-effect-level |

| Acronyms and Abbreviations | Definition |
|---|---|
| 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 |
| Acute ReV | acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements |
| Acute ReV-24hr | acute 24-hour health-based reference value for chemicals meeting minimum database requirements |
| Chronic $ReV_{threshold(nc)}$ | chronic health-based reference value for threshold dose response noncancer effects |
| RGDR | Regional Gas Dose Ratio |
| ROS | reactive oxygen species |
| RPF | relative potency factor |
| SA | surface area |
| SD | Sprague-Dawley |
| 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 |
| $UF_{Sub}$ | subchronic to chronic exposure uncertainty factor |
| $UF_L$ | LOAEL to NOAEL uncertainty factor |
| $UF_D$ | incomplete database uncertainty factor |

| Acronyms and Abbreviations | Definition |
|---|---|
| USEPA | United States Environmental Protection Agency |
| $V_E$ | minute volume |

# Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of diethanolamine (DEA) and triethanolamine (TEA), respectively, for use in air permitting and air monitoring. Please refer to the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) 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 the physical/chemical data of DEA and TEA.

**Table 1. Acute Health and Welfare-Based Screening Values for Diethanolamine and Triethanolamine**

| Screening Level Type | Duration | Value 1 (µg/m³) | Value 2 (ppb) | Usage | Flags | Surrogated/ RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Acute ReV | 1 h | 170 | -- | N | none | -- | Laryngeal inflammation and edema in rats. | Aerosol, treat as PM, based on 5-day TEA exposure study (Gamer et al. 2008). |
| Acute ReV-24hr | -- | -- | -- | -- | -- | -- | -- | -- |
| **$^{acute}$ESL** | **1 h** | **51** | **--** | **P** | **S, D** | **--** | **Same as above.** | **Same as above.** |
| $^{acute}$IOAEL | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{acute}ESL_{odor}$ | -- | -- | -- | -- | -- | -- | -- | Mild ammonia-like odor. |
| $^{acute}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No relevant data found. |

Bold values used for air permit reviews; DEA and TEA are not monitored for by the TCEQ's ambient monitoring program.

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

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

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

**Table 2. Chronic Health and Welfare-Based Screening Values for Diethanolamine and Triethanolamine**

| Screening Level Type | Duration | Value 1 (µg/m³) | Value 2 (ppb) | Usage | Flags | Surrogated/ RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Chronic $ReV_{threshold(nc)}$ | 70 yr | 25 | -- | N | None | -- | Increased relative liver weight in female rats. | Aerosol, treat as PM, ReV development documented in Haney et al. 2018. |
| **$^{chronic}ESL_{threshold(nc)}$** | **70 yr** | **7.5** | **--** | **P** | **S, D** | **--** | **Same as above.** | **Aerosol, treat as PM.** |
| $^{chronic}ESL_{threshold(c)}$ | -- | -- | -- | -- | -- | -- | -- | Data are inadequate for an assessment of human carcinogenic potential via the inhalation route. |
| $^{chronic}ESL_{nonthreshold(c)}$ | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{chronic}IOAEL(nc)$ | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{chronic}IOAEL(c)$ | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{chronic}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No relevant data found. |

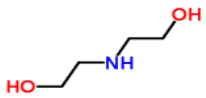
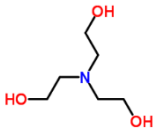
Bold values used for air permit reviews

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

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

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

**Table 3. Chemical and Physical Data**

| Parameter | Diethanolamine | Triethanolamine | Reference |
|---|---|---|---|
| Chemical Structure |  |  | ChemSpider 2016 |
| Molecular Formula | $C_4H_{11}NO_2$ | $C_6H_{15}NO_3$ | OEHHA 2001 |
| Molecular Weight | 105.14 | 149.22 | OEHHA 2001; ACGIH 2001 |
| Physical State at 25°C | Solid (liquid above 28°C) | Viscous liquid | ACGIH 2001 |
| Color | Colorless | Colorless to pale yellow | ACGIH 2001 |
| Odor | Mild-ammonical | Slight ammonia-like | ACGIH 2001 |
| CAS Registry Number | 111-42-2 | 102-71-6 | ACGIH 2001 |
| Common Synonym(s) | DEA; 2,2'-iminodiethanol; 2,2'-iminobisethanol; 2,2'-aminodiethanol. | TEA; 2,2',2"-nitrilotriethanol | OEHHA 2001 |
| Solubility in water | Soluble in alcohol, water, acetone | Soluble in chloroform, benzene, and ether; miscible with acetone, methanol, and water | OEHHA 2001; ACGIH 2001 |
| Log $K_{ow}$ | -1.43 | -1.00 | HSDB 2016 |
| Vapor Pressure | < 0.01 torr at 20°C | < 0.01 torr at 20°C | ACGIH 2001 |
| Conversion Factors | 1 mg/m$^3$ = 0.23 ppm<br>1 ppm = 4.29 mg/m$^3$ | 1 mg/m$^3$ = 0.16 ppm<br>1 ppm = 6.09 mg/m$^3$ | ACGIH 2001 |

# Chapter 2 Background Information

## *2.1 Physical/Chemical Properties*

The primary physical and chemical properties of DEA and TEA are summarized in Table 3.

## *2.2 Sources and Uses*

DEA is a colorless solid at room temperature and a liquid above 28°C, while TEA is a liquid above 20.5°C. Both have a mild ammonia-like odor and are soluble in most polar solvents. DEA and TEA are produced by reacting 2 or 3 moles, respectively, of ethylene oxide with ammonia (Knaak et al. 1997). DEA and TEA share similar physical chemical properties and are often used in mixtures of other alkanolamines varying physical chemical properties (e.g., vapor pressures). These mixtures are used in a wide range of applications, including industrial uses such as metal working fluids (MWFs) and corrosion inhibitors, and commercial uses such as soaps, cosmetics, shampoos, and hair conditioners (IARC 2013). Due to their low vapor pressure, the most common route of exposure to DEA and TEA is through dermal contact, although workers may be exposed through inhalation of aerosols (Gamer et al. 2008).

# Chapter 3 Acute Evaluation

The Development Support Document (DSD) is a summary of the key and supporting studies and procedures used by the TCEQ to derive inhalation toxicity values. This section is based on a review of current literature and background information found from a search of publicly available databases (TCEQ 2015). A systematic review was conducted and is detailed in Appendix 1. Due to the similar chemical structures, physical/chemical properties, observed effects, and mixtures that often contain both DEA and TEA, a single acute ReV and $^{acute}$ESL was derived that is applicable to both chemicals and any mixtures thereof (Gamer et al. 2008).

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

The majority of the toxicity data on DEA and TEA stems from studies on the exposure of industrial workers to fluids containing DEA and/or TEA, such as MWFs. Exposure via inhalation is less common and appears to be much less significant toxicologically than exposure through dermal contact. Fewer studies have examined the effects of inhalation to DEA and TEA compared to dermal exposure.

### 3.1.1 Key and Supporting Studies

Much of the available toxicity literature focuses on worker exposure to mixtures containing DEA and/or TEA. Very few studies examine exposure to pure DEA or TEA, and studies tend to lack important information such as exposure concentrations and possible dermal exposures. This

review will focus on the available inhalation data, because the purpose of the DSD is to derive inhalation (not oral or dermal) toxicity factors.

### *3.1.1.1 Human Studies*

#### 3.1.1.1.1 Piipari et al. (1998)

Piipari et al. (1998) examined a case of DEA-induced occupational asthma in a patient that routinely handled cutting fluid containing DEA (0.15%) and TEA (0.32%). The patient was a 39-year-old male metal worker who began experiencing respiratory symptoms 1-2 years after the heated cutting fluid was introduced, including sinusitis, bronchitis, cough, sneezing, breathlessness, and wheezing. These symptoms only occurred on work days and increased towards the end of the work day. The study authors conducted bronchial provocation tests in an isolated exposure chamber (6 $m^3$) using cold and heated cutting fluid and pure DEA at concentrations of 0.75 and 1 $mg/m^3$. TEA was not tested. DEA was aerosolized using compressed air and a sprayer for 10 seconds, and the exposure lasted for 15 minutes (min). DEA concentrations were measured using high pressure liquid chromatography, and the reported concentrations are the means of the two measurements done during both DEA challenges. This was followed up by forced expiratory volume in 1 second ($FEV_1$) tests that measure lung function, and the authors considered a drop of 20% or more in $FEV_1$ to be adverse. No symptoms were observed following exposure to the cold cutting fluid (concentration unknown) for 30 min. Heated cutting fluid in a 1:1 dilution with water (concentration unknown) resulted in a 20% decrease in $FEV_1$ along with wheezing and breathlessness 1 hour (h) after challenge, while exposure to undiluted heated cutting fluid resulted in a 23% decrease in $FEV_1$ along with wheezing and breathlessness 2 h after challenge. DEA aerosol at 0.75 $mg/m^3$ for 15 min caused a suggestive adverse association/reaction, with a maximum $FEV_1$ drop of 14% with mild suggestive breathlessness, and no audible wheezing 45 min after challenge. DEA aerosol at 1 $mg/m^3$ for 15 min caused an adverse reaction, with a maximum $FEV_1$ drop of 27% and suggestive breathlessness, with no abnormal auscultatory findings (i.e., audible wheezing) 7 h after challenge. This study was unsuitable for the derivation of an acute ReV because it only examined a single subject who had been previously sensitized to DEA and experienced on-going symptoms due to long-term exposure (i.e., not acute or even subacute) to unknown but perhaps significantly higher concentrations.

#### 3.1.1.1.2 Savonius et al. (1994)

Savonius et al. (1994) examined two metal workers with occupational asthma who handled cutting fluid containing TEA. Chamber experiments were performed and several respiratory function tests were conducted, including nonspecific bronchial reactivity, asthma provocation, peak expiratory flow (PEF) for 24 h, and $FEV_1$ tests. Challenges with cutting fluid were performed with the patient stirring 200 milliliters of either cold or heated fluid for 30 min. Air concentrations were not measured. The author's considered a drop of over 20% in PEF values

within 1 h (immediate reaction) or 24 h (delayed reaction) to be an adverse response. Two control asthmatic patients were exposed to TEA but neither showed any symptoms.

- Patient 1 had been working at his job since 1967, and the cutting fluid used was composed of 85% TEA. The patient began experiencing shortness of breath and cough during work days, worsening by the end of the week (wk). Chamber challenges were performed with polyol (control), cutting fluid that did not contain TEA, and cold or heated TEA-containing cutting fluid. Cold TEA-containing cutting fluid caused an immediate, long-lasting PEF drop of 18%. Heated TEA-containing cutting fluid caused an immediate, long-lasting reaction with a PEF drop of 21%, and a decrease of 13% in $FEV_1$.
- Patient 2 had worked as a metal worker for 34 years. He experienced cough, dyspnea, chest tightness, rhinitis, and eye irritation at work. Initially the symptoms subsided when he was not at work, but later the symptoms did not improve during his off time. PEF surveillance for 2 wk showed values typical of occupational asthma. A chamber challenge with heated turning fluid containing 14% TEA caused wheezing and an immediate PEF drop of 17%. Challenge with cold pure TEA caused an immediate PEF drop of 21%.

TEA exposure concentrations were not measured (and workers experienced on-going symptoms of occupational asthma due to chronic exposure to perhaps significantly high concentrations), making this study unsuitable for the identification of a NOAEL/LOAEL.

### *3.1.1.2 Animal Studies*

#### 3.1.1.2.1 Gamer et al. (2008)

Groups of male and female Wistar rats were exposed nose-only to DEA (10/sex/group for 2 wk) or TEA (5/sex/group for 5 d) at target concentrations of 0, 100, 200, and 400 mg/m$^3$ for 6 h/day for 10 and 5 exposures, respectively. These 2 wk and 5 d exposures served as a range finding study for chronic (DEA) and subacute/subchronic (TEA) studies. The main TEA study was a 28-d study, so this subacute/subchronic study is described in more detail below. Details about the clinical and pathological examinations for the subacute range-finding study were sparse.

DEA 2-wk study – No substance-related effects were observed in rats exposed to 100 or 200 mg/m$^3$. Exposure to 400 mg/m$^3$ resulted in decreased body weight gain in males and slightly decreased serum cholesterol in females. Relative and absolute liver weights were also increased in females. No histopathological effects were observed in the respiratory tracts at any of the concentrations examined, including the nasal cavity, trachea, and lungs. The authors state that examination of the larynx was not included in the range finding study, although the subchronic study identified laryngeal effects as a sensitive endpoint. A NOAEL of 200 mg/m$^3$ and a LOAEL of 400 mg/m$^3$ for decreased body weight gain in males and slightly decreased

serum cholesterol and increased relative and absolute liver weights in females were identified from this study.

TEA 5-d study – No clinical, hematological, or pathological effects were observed at any of the concentrations tested. Concentration-dependent laryngeal inflammation and edema were observed histopathologically at 200 and 400 mg/m$^3$. A NOAEL of 100 mg/m$^3$ and a LOAEL of 200 mg/m$^3$ TEA for laryngeal inflammation and edema were identified from this study.

TEA 28-d study - Groups of male and female rats (10/sex/group) were exposed to targeted TEA concentrations of 20, 100, and 500 mg/m$^3$ for 6 h/d for 20 workdays over a period of 28 days. No deaths occurred in any of the exposure groups, and no signs of clinical or neurological effects were observed in the two low dose groups. Bloody crusts were observed on the nasal edges of the animals exposed to 500 mg/m$^3$ TEA. No treatment-related alterations in body weights, organ weights, clinical chemistry, or hematology were observed. Focal minimal to moderate inflammation in the submucosa of the larynx was histopathologically observed in a concentration-dependent manner in both male (20, 100, and 500 mg/m$^3$) and female (100 and 500 mg/m$^3$) rats. No other histopathological or neuropathological effects were observed. A minimal subacute LOAEL of 20 mg/m$^3$ was identified.

### *3.1.1.3 Reproductive and Developmental Studies*

In Gamer et al. (1993), groups of 25 pregnant Wistar rats were exposed nose-only for 6 h/d on gestational days (GD) 6-15 to a liquid aerosol of DEA at 10, 50 and 200 mg/m$^3$. Maternal toxicity, indicated by vaginal hemorrhage in 8 of the dams on GD 14, and fetotoxicity, evidenced by a statistically significant ($p<0.05$) increased incidence of total fetal skeletal variations, were observed at 200 mg/m$^3$. No teratogenic effects were seen at any level. The 6-h LOAEL of 200 mg/m$^3$ DEA, however, is equal to the 6-h LOAEL of 200 mg/m$^3$ TEA for laryngeal inflammation and edema (Gamer et al. 2008) and application of the regional deposited dose ratio (RDDR) for these systemic effects would cause the point of departure (POD) human equivalent concentration ($POD_{HEC}$) corresponding to the reproductive/developmental LOAEL to be significantly higher than that based on laryngeal effects.

A few studies have been conducted using other routes of exposure, such as oral or dermal, but the dose received by other routes are significantly higher than can be achieved via inhalation. NTP (1992) observed testicular degeneration in male F344/N rats administered 10,000 ppm DEA in drinking water for 2 wk (1016 mg/kg/d based on water consumption rates). Using route-to-route extrapolation and assuming that a 70 kg person inhales 20 m$^3$ of air per day, the corresponding HEC is ≈3550 mg/m$^3$, an estimated LOAEL, which is significantly higher than the 5-d LOAEL of 200 mg/m$^3$ from the Gamer et al. (2008) study, and application of the RDDR to estimate the HEC for laryngeal effects would further increase the difference. Price et al. (2005) identified an oral NOAEL of 50 mg/kg/d and a LOAEL of 125 mg/kg/d for maternal and

developmental toxicity in SD rats administered DEA from GD 6-19. The equivalent inhalation exposure concentrations are 175 and 437.5 mg/m$^3$, respectively, and application of the RDDR for these systemic effects to estimate a $LOAEL_{HEC}$ would further increase the difference compared to a $LOAEL_{HEC}$ based on laryngeal effects. Therefore, the identified 5-d TEA NOAEL of 100 mg/m$^3$ for laryngeal effects is considered protective of potential reproductive and developmental effects.

## 3.1.2 Metabolism and Mode of Action (MOA) Analysis

Although the local irritant effects observed following inhalation exposure to DEA or TEA are thought to be due to the alkaline properties of these amines (Gamer et al. 2008), the MOA(s) for laryngeal inflammation and edema remains unknown. The only available dose metric is the air concentration of DEA.

## 3.1.3 Health-Based Acute 1-h ReV and ESL

### *3.1.3.1 Selection of the Key Study, Point of Departure (POD), and Critical Effect*

### *3.1.3.2 MOA and Dose Metric for Critical Effect*

Gamer et al. (2008) identified a NOAEL of 100 mg/m$^3$ and a LOAEL of 200 mg/m$^3$ for laryngeal inflammation and edema following a 5-d exposure to TEA. The long-term exposure of rodents to DEA has also shown the larynx to be a sensitive target for these amines (e.g., Haney et al. 2018). Therefore, the NOAEL of 100 mg/m$^3$ for laryngeal inflammation and edema observed in the 5-d TEA study will be used as the POD for derivation of the acute 1-h ReV and ESL for both DEA and TEA.

### *3.1.3.3 Adjustments to the POD*

#### 3.1.3.3.1 Default Exposure Duration Adjustments

The effects of DEA and TEA are assumed to be concentration- and duration-dependent. Animals were exposed to TEA for 6 h/d for 5 d; however, a single day of exposure will conservatively be used as the exposure duration. The 6-h exposure duration ($C_1$) was adjusted to a $POD_{ADJ}$ of 1-h exposure duration ($C_2$) using Haber's Rule as modified by ten Berge (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3:

$$POD_{ADJ} = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$POD_{ADJ} = [(100 \text{ mg/m}^3)^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$POD_{ADJ} = 181.7120 \text{ mg/m}^3$$

#### 3.1.3.3.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Default dosimetric adjustments from animal-to-human exposure were conducted for the Gamer et al. (2008) study to determine the calculated $POD_{HEC}$. The Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research and National Institute for Public Health and the Environment (RIVM) 2004 multiple path particle dosimetry model (MPPD) v 3.0 program (CIIT and RIVM 2004; Asgharian et al. 2014) was used to calculate the deposition fraction of TEA in the target respiratory region.

Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions. The mean mass median aerodynamic diameter (MMAD) for each chamber ranged from 0.7 – 1.1 µm with a geometric standard deviation (GSD) of 2-3 µm (Gamer et al. 2008). For the MPPD model, the high end was used for both parameters (MMAD = 1.1 µm; GSD = 3). For particle density, the default value of 1 $g/cm^3$ was used.

For the RDDR calculations, the default minute ventilation (VE) for humans (13,800 mL/min) given by USEPA (1994) was used. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values that correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) were used to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model. The calculated human tidal volume is 842.74 ml/breath and the breathing frequency is 16.375 breaths per minute. Except for the parameter values discussed above, all remaining values used were default (refer to Appendix 2).

Since no body weight data were available for the 5-day TEA exposure study, the minute volume was calculated based on the body weight for male (268 grams) and female rats (187 grams) observed in the TEA study at Day 1 for exposure at 100 $mg/m^3$. The average body weight was 227.5 grams and the calculated minute volume was 166.364 mL/min (USEPA 1994). The chemical concentration is the $POD_{ADJ}$ of 181.7120 $mg/m^3$. The target region for TEA was considered to be the total particle distribution in the larynx. The head/extrathoracic surface areas for humans (200 $cm^2$) and rats (15 $cm^2$), used as the normalizing factors, were taken from the EPA reference concentration guidance (USEPA 1994). Once the deposition fractions for the rat ($DF_A$ = 0.3911) and human ($DF_H$ = 0.3634) were determined (Appendix 3), the regional deposited dose ratio (RDDR) was calculated as follows:

$$RDDR = [\ (V_E)_A/(V_E)_H\ ] \times [\ DF_A/\ DF_H\ ] \times [\ NF_H/\ NF_A\ ]$$

where: $V_E$ = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor

A = animal
H = human

$RDDR = [166.364\ mL/min / 13{,}800\ mL/min] \times [0.3911/0.3634] \times [200\ cm^2/15\ cm^2]$
$RDDR = 0.1730$

The RDDR was then used to derive a human equivalent concentration POD ($POD_{HEC}$).

$POD_{HEC} = POD_{ADJ} \times RDDR = 181.7120\ mg/m^3 \times 0.1730$
$POD_{HEC} = 31.436\ mg/m^3$

### *3.1.3.4 Adjustments to the $POD_{HEC}$*

The $POD_{HEC}$ based on a NOAEL from the Gamer et al. (2008) study was used and UFs were applied to derive the acute ReV (i.e., assuming a threshold MOA for a noncarcinogenic endpoint). The following UFs were applied to the $POD_{HEC}$ of 31.436 $mg/m^3$: 10 for intraspecies variability ($UF_H$), 3 for interspecies variability ($UF_A$), and 6 for database uncertainty ($UF_D$).

- A $UF_H$ of 10 was used to account for variation in sensitivity among the members of the human population including possible child/adult differences, those with pre-existing medical conditions, etc.;
- A $UF_A$ of 3 was used to account for potential pharmacodynamic differences between animals and humans (pharmacokinetic adjustment was already performed); and
- A $UF_D$ of 6 was used because there was only a single range-finding animal study available that was suitable for the derivation of an acute ReV for DEA or TEA. Data from the available reproductive/developmental inhalation and oral studies suggest that the POD is protective for potential reproductive/developmental effects. Although the quality of the overall Gamer et al. (2008) study was high, the quality of the range-finding portion of the study used as the POD is considered medium due to differences in study design (fewer animal numbers, fewer dose groups, critical endpoints not examined), and the confidence in the acute database is low.

Acute 1-h $ReV = POD_{HEC} / (UF_H \times UF_A \times UF_D)$

$= 31.436\ mg/m^3 / (10 \times 3 \times 6)$
$= 31.436\ mg/m^3 / 180$
$= 0.1746\ mg/m^3$
$= 174.6\ \mu g/m^3$ or $170\ \mu g/m^3$ (rounded to two significant digits)

### *3.1.3.5 Health-Based 1-h Acute ReV and $^{acute}$ESL*

The resulting 1-h acute ReV was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the $^{acute}$ESL at the target hazard quotient (HQ) of 0.3 (Table 4).

**Table 4. Derivation of the 1-h Acute ReV and $^{acute}$ESL**

| Parameter | Summary |
|---|---|
| Study | Gamer et al. 2008 |
| Study Population | Male and female Wistar rats (5-10 animals/group) |
| Study Quality | Medium (Range-finding study) |
| Exposure Method | Inhalation |
| Exposure Duration | 0, 100, 200, and 400 mg/m$^3$ for 6 h/day for 10 (DEA) and 5 (TEA) exposures |
| Critical Effects | Laryngeal inflammation and edema |
| NOAEL | 100 mg/m$^3$ TEA |
| LOAEL | 200 mg/m$^3$ TEA |
| $POD_{ADJ}$ | 181.7120 mg/m$^3$ |
| $POD_{HEC}$ | 31.436 mg/m$^3$ |
| Total uncertainty factors (UFs) | 180 |
| *Interspecies UF* | 10 |
| *Intraspecies UF* | 3 |
| *Incomplete Database UF*<br>*Database Quality* | 6<br>Low |
| **Acute ReV [1 h] (HQ = 1)** | **170 µg/m$^3$** |
| **$^{acute}$ESL [1 h] (HQ = 0.3)** | **51 µg/m$^3$** |

## *3.2 Welfare-Based Acute Evaluation*

## 3.2.1 Odor Perception

DEA and TEA have a mild ammonia-like odor, and therefore, no odor values were derived.

### 3.2.2 Vegetation Effects

After a literature review, there was no data found on any adverse effects of DEA or TEA on vegetation.

## *3.3 Summary of the Acute Values*

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

- acute ReV = 170 µg/m$^3$
- $^{acute}$ESL = 51 µg/m$^3$

Although we do not currently monitor for DEA or TEA, the acute ReV of 170 µg/m$^3$ may be used in the evaluation of ambient air monitoring data in the future. The short-term ESL used for air permit reviews of TEA and DEA is the health-based $^{acute}$ESL of 51 µg/m$^3$.

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential*

### 4.1.1 Key and Supporting Studies

Haney et al. (2018) documents the methods and rational used by the TCEQ for derivation of a chronic ReV for DEA. The chronic ReV is based on a critical toxicological evaluation of results reported in three animal inhalation studies by Gamer et al. (1993, 1996, 2008) as well as other relevant information (e.g., criteria relevant to endpoint adversity, TCEQ guidance, developmental/reproductive toxicity results for other exposure routes). Ultimately, the ReV (25 µg/m$^3$) was based on statistically significantly increased relative liver weight in female Wistar rats in Gamer et al. (2008) as the critical effect. Briefly, the lower confidence limit on the benchmark dose ($BMDL_{10}$ of 5.5 mg/m$^3$) was adjusted to an HEC and to continuous exposure before dividing the final point of departure (2.3 mg/m$^3$) by a total uncertainty factor of 90, which considered standard key areas of uncertainty (i.e., intrahuman variability, potential interspecies toxicodynamic differences, database limitations) (Table 5). While laryngeal effects observed in Gamer et al. (2008) were also considered as candidate critical effects, toxicological evaluation of the adversity and human relevance of rat laryngeal squamous metaplasia and concomitant effects at the various exposure levels resulted in identifying a LOAEL for laryngeal squamous hyperplasia and chronic inflammation, which was much higher than the liver weight LOAEL identified. The chronic ReV of 25 µg/m$^3$ is considered health protective for the general population and can be used to evaluate the potential adverse health effects of long-term environmental exposure of the general public to DEA and/or TEA (i.e., long-term, ambient air dispersion modelling or monitoring data) Haney et al 2018 serves as the detailed

documentation of the assessment of the noncarcinogenic potential of DEA for the purposes of this DSD.

### 4.1.2 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, and then used to calculate the $^{chronic}ESL_{threshold(nc)}$ using a target hazard quotient of 0.3.

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

| Parameter | Summary |
|---|---|
| Study | Gamer et al. 2008 |
| Study Population | Male and female Wistar rats (10-13 animals/group) |
| Exposure Method | Inhalation |
| Critical Effects | Increased relative liver weight in female rats. |
| Exposure Duration | 99 d |
| POD ($BMDL_{10\text{-}HEC}$) | 12.9 mg/m$^3$ |
| $POD_{HEC\text{-}ADJ}$ | 2.3 mg/m$^3$ |
| Total UFs | 90 |
| *Interspecies UF* | 10 |
| *Intraspecies UF* | 3 |
| *Subchronic to chronic UF* | 1 |
| *Incomplete Database UF*<br>*Database Quality* | 3<br>Medium |
| **Chronic ReV (HQ = 1)** | **25 µg/m$^3$** |
| **$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)** | **7.5 µg/m$^3$** |

## *4.2 Carcinogenic Potential*

The International Agency for Research on Cancer (IARC) classified DEA as a possibly carcinogen to humans (Group 2B) based on rodent dermal application studies conducted by the National Toxicology Program (NTP 1992). IARC determined that there is inadequate evidence in humans for the carcinogenicity, while there is sufficient evidence in experimental animals for the carcinogenicity of DEA. To date, there are no human or animal inhalation studies indicating that DEA or TEA alone are carcinogenic by the inhalation route. More specifically, there is not a well-

conducted chronic inhalation carcinogenicity study, which could be used to conduct dose-response modeling. Consequently, a chronic carcinogenic inhalation value cannot be and was not developed.

## *4.3 Welfare-Based Chronic Evaluation*

### 4.3.2 Vegetation Effects

No data were found regarding long-term vegetation effects.

## *4.4 Summary of the Chronic Values*

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

- Chronic ReV = 25 µg/$m^3$
- $^{chronic}ESL_{threshold(nc)}$ = 7.5 µg/$m^3$

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 7.5 µg/$m^3$. Although we do not currently monitor for DEA or TEA, the chronic ReV of 25 µg/$m^3$ could be used for the evaluation of ambient air monitoring data in the future. The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) would not be used to evaluate ambient air monitoring data.

## Chapter 5 References

ACGIH (American Conference of Government Industrial Hygienists). (2001). Diethanolamine. In Documentation of the threshold limit values and biological exposure indices, 7th Ed. ACGIH, Cincinnati, OH.

ACGIH (American Conference of Government Industrial Hygienists). (2001). Triethanolamine. In Documentation of the threshold limit values and biological exposure indices, 7th Ed. ACGIH, Cincinnati, OH.

Gamer, A.O., Rossbacher, R., Kaufmann, W. and van Ravenzwaay, B. 2008. The inhalation toxicity of di- and triethanolamine upon repeated exposure. Food and Chemical Toxicology. 46: 2173-2183.

Gamer, A., Hellwig, J., Hildebrand, B., 1993. Study of the prenatal toxicity of diethanolamin in rats after inhalation. BASF Project No. 31RO233/90010. Ludwigshafen, FRG: BASF.

Gamer, A., Mellert, W., Leibold, E., et al., 1996. Diethanolamin – Subchronic inhalation toxicity and neurotoxicity study in Wistar rats 90-day liquid aerosol exposure. BASF Project No. 50I0075/93011. Ludwigshafen, FRG: BASF.

Haney, J.T., McCant, D., Honeycutt, M.E., and Lange, S. 2018. Development of an inhalation reference concentration for diethanolamine. Regulatory Toxicology and Pharmacology. 92:55-66. http://www.sciencedirect.com/science/article/pii/S0273230017303689

Hazardous Substance Data Base. 2016. Diethanolamine and Triethanolamine. Accessed May 12, 2016. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~ouE1WN:3

International Agency for Research on Cancer (IARC). 2013. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 101. Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water.

Knaak, J.B., Leung, H.W., Stott, W.T., Busch, J. and Bilsky, J. 1997. Toxicology of mono-, di-, and triethanolamine. Reviews of Environmental Contamination and Toxicology. 149: 1-86.

NTP. 1992. Technical Report on Toxicity Studies of Diethanolamine (CAS No. 111-42-2). Administered Topically and in Drinking Water to F344/N Rats and B6C3F1 Mice. NIH Publication No. 92-3343 October 1992.

Office of Environmental Health Hazard Assessment (OEHHA). 2001. Determination of noncancer chronic reference exposure levels batch 2B December 2001. Chronic toxicity summary Diethanolamine. A-27 – A-33.

Piipari, R., Tuppurainen, M., Tuomi, T., Mantyla, L., Henriks-Eckerman, M., Keskinen, H. and Nordman, H. 1998. Diethanolamine-induced occupational asthma, a case report. Clinical and Experimental Allergy. 28: 358-362.

Price, C.J., Marr, M.C., Myers, C.B., Jahnke, G.D. 2005. Postnatal development of rat pups after maternal exposure to diethanolamine. Birth Defects Res B Dev Reprod Toxicol. 74(3):243-54.

Savonius, B., Keskinen, H., Tuppurainen, M. and Kanerva, L. 1994. Occupational Asthma caused by ethanolamines. Allergy. 49: 877-881.

TCEQ. 2015. Texas Commission on Environmental Quality. Guidelines to develop effects screening levels, reference values, and unit risk factors. RG-442. Chief Engineer's Office.

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

# Appendix 1 Systematic Review and Evidence Integration

## *A.1 Problem Formulation and Protocol*

Problem formulation identifies and defines the causal questions and describes the extent of the evaluation. These questions structured the systematic review:

- What are the physical and chemical properties?
- What is the critical effect following exposure?
- Are the doses that cause the critical effect environmentally relevant?
- Are there sensitive subpopulations?
- What is the mode of action (MOA)?
- Does route of exposure play a role?
- Is it carcinogenic, and if so, is it carcinogenic by a specific route of exposure?
- Is it a reproductive or developmental toxicant?

Protocol development is another important aspect in the initial process. A protocol is typically developed around a PECO statement: Populations, Exposure, Comparator/Control, and Outcomes. These identifiers are used to lay out the framework for the literature search and inclusion/exclusion criteria. The PECO statement followed these criteria:

**Table 6. PECO statement used by the TCEQ to develop toxicity factors**

| | |
|---|---|
| Population | General human population and any relevant sensitive subpopulations, animals, and vegetation |
| Exposure | Exposure to DEA/TEA, surrogates with demonstrated similar MOAs, and any identified metabolites |
| Comparator/ Control | Populations exposed to concentrations below the concentration that causes the most sensitive critical effect |
| Outcome(s) | The most sensitive critical effect directly related to DEA/TEA exposure |

The protocol used for the systematic review and the development of toxicity factors for DEA/TEA is as follows:

1. Identify the chemical of interest and define the causal questions
2. Conduct a systematic review
    a) Conduct a systematic literature search
    b) Identify the inclusion/exclusion criteria
    c) Extract the relevant data from each data stream (human, animal, mechanistic)
    d) Assess the study quality and conduct a risk of bias analysis

e) Weigh the evidence in each data stream and then integrate the evidence across the data streams
f) Rate the confidence in the evidence

3. Derive toxicity factors (TCEQ 2015)
    a) Review the essential data, including chemical/physical properties and selected key studies from the systematic review
    b) Conduct MOA analysis
    c) Choose the appropriate dose metric considering toxicokinetics and MOA
    d) Select critical effect, based on human equivalent exposure considering each key study
    e) Extrapolate from the adjusted POD to lower exposures based on MOA analysis

## *A.2 Systematic Literature Review and Study Selection*

As a first step, publicly available databases were searched using explicitly stated search criteria. Please see TCEQ (2015) for a list of available databases that were searched. The search terms used in literature review, along with the number of results from PubMed, are found in Table 7. Additional references were also identified using the reference sections from some of the selected studies. This literature review was conducted in June, 2015, and therefore studies published after this date were not available at the time of the review.

**Table 7. Search strings used in the literature review**

| Search Term/String | PubMed Results |
|---|---|
| diethanolamine | 495 |
| triethanolamine | 1100 |
| diethanolamine OR triethanolamine | 1524 |
| (diethanolamine OR triethanolamine) AND (inhal* OR air OR vapor OR aerosol OR oral) | 186 |
| (diethanolamine OR triethanolamine) AND (inhal* OR air OR vapor OR aerosol) | 94 |

Following this initial review, which produced a pool of ~170 articles and documents, specific inclusion and exclusion criteria were used to narrow down the pool of available data. The criteria along with examples of the kinds of studies that were excluded can be found in Table 8.

**Table 8. Inclusion/exclusion criteria used in the review of DEA and TEA**

| Study Type | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| General | Complete study available for review | - Only abstract is available<br>- Study in a language other than English<br>- Unpublished report/unable to retrieve |
| | Exposure concentration is environmentally relevant | - Significantly high concentrations used<br>- Study focused on overdose/poisoning or mortality<br>- Exposure concentration unknown |
| | Study contains original data | - Study is a review article |
| | Study examines effects related to chemical exposure | - Study measures concentration in products, etc.<br>- Study does not examine health effects |
| | Study focused on the chemical of concern or active metabolites | - Study examined mixture effects<br>- Study on treatment following exposure |
| Animal | Route of exposure is relevant to environmental exposure and to toxicity factor development | - Exposure through i.v., i.p., or subcutaneous injection<br>- Study examining dermal exposure<br>- Study examining oral exposure* |
| | Relevant animal model and endpoints examined | - Study used non-mammalian animal models<br>- Endpoint studied not relevant to human health<br>- Endpoint not applicable to toxicity factor development |
| Human/Epi | Route of exposure is relevant to toxicity factor development | - Study examining dermal exposure<br>- Study examining oral exposure*<br>- Multiple routes possible/unknown route of exposure |
| | Relevant endpoints examined | - Study focused on mortality/intentional ingestion |

i.v. – intravenous, i.p. – intraperitoneal

* Studies using the oral route of exposure were initially excluded from the key study selection due to the inhalation route being more applicable to the development of a ReV/ESL. Oral data may be used to fill gaps in the inhalation data as needed.

Using these inclusion/exclusion criteria, the pool of available data was narrowed down to 8 included studies: human studies and 3 animal studies. These studies were collected and reviewed in detail by each of the authors.

## *A.3 Data Extraction*

Each of the identified studies was reviewed in detail and the primary data was extracted for potential use in this DSD. Data from the studies can be found in Table 9 (human studies) and Table 10 (animal studies). Data that was applicable to the development of the acute and chronic ReVs and ESLs are also in sections 3.1.1 and 4.1.1, respectively.

**Table 9. Data extraction from human studies**

| Reference | Exposure Concentration | Exposure Duration | NOAEL | LOAEL | Notes |
|---|---|---|---|---|---|
| Henriks-Eckerman et al. (2007) | 57 µg/m$^3$ DEA<br>6 µg/m$^3$ TEA | Varied | -- | -- | Personal air sampling, health effects not measured or reported |
| Herman (1983) | Unknown concentration of TEA | Varied | -- | -- | Sensitized subject, possible dermal exposure |
| Levin et al. (1994) | <0.02-0.5 mg/m$^3$ total amines | Varied | -- | -- | Personal air sampling, health effects not measured or reported |
| Lillienberg et al. (2008) | 0.001-0.063 mg/m$^3$ TEA | Varied | -- | -- | Personal air sampling, health effects not measured or reported |
| Piipari et al. (1998) | 0.75, 1 mg/m$^3$ DEA | 15 min | 0.75 mg/m$^3$ | 1 mg/m$^3$ | Decrease in $FEV_1$, single sensitized subject |
| Savonius et al. (1994) | Unknown concentration of TEA | 30 min | -- | -- | Decrease in PEF, exposure concentrations not measured |
| Yacher et al. (2000) | 0.03-0.25 mg/m$^3$ TEA | Varied | -- | -- | Personal air sampling, health effects not measured or reported |

**Table 10. Data extraction from animal studies**

| Reference | Species | Exposure Concentration | Exposure Duration | NOAEL (mg/m3) | LOAEL (mg/m3) | Notes |
|---|---|---|---|---|---|---|
| Gamer et al. (1993) | Rats | 10, 50, and 200 mg/m$^3$ DEA | 6 h/d for 2 wk (10 exposures) | 50 | 200 | Maternal toxicity and embryo-fetal effects |
| Gamer et al. (1996) | Rats | 15, 150, and 400 mg/m$^3$ DEA | 6 h/d for 90 days (65 exposures) | 15 | 150 | Statistically increased relative liver weight in female rats |
| | | 15, 150, and 400 mg/m$^3$ DEA | 6 h/d for 90 days (65 exposures) | -- | 15 | Squamous metaplasia of the epithelial surface in the larynx [a] |
| Gamer et al. (2008) | Rats | 100, 200, and 400 mg/m$^3$ DEA | 6 h/d for 2 wk (10 exposures) | 200 | 400 | Decreased body weight and body weight gain in males and slightly decreased serum cholesterol and increased relative and absolute liver weights in females |
| | | 100, 200, and 400 mg/m$^3$ TEA | 6 h/d for 5 d | 100 | 200 | Laryngeal inflammation and edema |
| | | 1.5, 3, 8, 15, 150, and 400 mg/m$^3$ DEA | 6 h/d, 5 d/wk over 99 d | 1.5 | 3 | Focal squamous metaplasia of the laryngeal epithelium [a] |
| | | 20, 100, and 500 mg/m$^3$ TEA | 6 h/d, 5 d/wk over 28 d | -- | 20 | Focal squamous metaplasia of the laryngeal epithelium in male rats |

## *A.4 Study Quality and Risk of Bias (ROB)*

Each of the selected studies was evaluated for study quality and ROB based on a number of attributes determined prior to this review. The attributes were scored on a scale of 1 to -1, with 1 meaning the study possessed the specific attribute, 0 meaning the study did not examine the attribute, and -1 meaning the study lacked the attribute. Each of these study quality attributes along with the criteria used in scoring them can be found in Table 11 (general studies), Table 12 (human studies) and Table 13 (animal studies).

**Table 11. Study quality and ROB scoring criteria for general studies**

| Score Criteria | 1 | 0 | -1 |
|---|---|---|---|
| Original data | Authors generated primary data | Authors used data from another source to draw their own conclusions | Review study, data from other sources mentioned but not further analyzed |
| Applicable route of exposure | Study looks at specific route of exposure relevant to ReV development | Unknown what the exact route of exposure was | Study states that a different route of exposure was studied |
| Single route of exposure | Study looks at a single route of exposure relevant to ReV development | Unknown if multiple routes were accounted for during exposure | Study states that multiple routes were examined |
| Single chemical exposure | Single chemical of interest or activate metabolite was used | Unknown whether additional chemicals may have been present | Study used multiple chemicals/mixture |
| Range of doses/ exposures | Study examines >2 exposure concentrations | Study examines one or two exposure concentrations | Exposure concentration unknown |
| Exposure concentration known/ measured | Study measures the exposure concentration (analytical) | Exposure concentration assumed but not measured/tested (nominal) | Exposure concentration unknown |
| Blinded study | Study specifically states that blind testing was used | Unclear whether blind testing was used | Study specifically states that blind testing was not used |
| Health effects relevant to ReV development | Measured health effects relevant to ReV development | Measured effects not relevant to ReV development (e.g. measured changes in protein expression, urinary excretion) | No health effects were measured (e.g. measured air or mixture concentrations) |
| Appropriate endpoints measured | Study examines target organ or adverse effects known or suspected in be involved in MOA | Study lacks information about certain relevant endpoints (e.g. measured urinary excretion but not irritation or other effects) | Appropriate endpoints not measured (study did not examine adverse effects or effects not part of MOA) |
| Measured outcomes reported | All measured outcomes were reported in a consistent manner | Some outcomes were reported, but not consistently | All measured outcomes were not reported |
| Study design sufficient/ clearly defined | Study designed clearly defined and detailed in methods | Study design not defined, detailed information not provided | Study design contains an obvious flaw or problem |
| Calculation of sample size | Study conducts calculation to determine appropriate sample size | Study does not calculate sample size but sample size appears to be appropriate | Study does not calculate sample size and size does not appear to be sufficient |
| Confounding factors | Study eliminates or controls for any possible confounding factors | Confounding factors not identified or addressed | Study has confounding factors (e.g. smoking, behavioral patterns) |
| Appropriate research practices | Study provides enough detail to assume quality, uniformity, consistency, and reproducibility | Study qualities not clearly or specifically stated | Study lacks a specific aspect of quality, uniformity, consistency, or reproducibility |

**Table 12. Study quality and ROB scoring criteria for human studies**

| Score Criteria | 1 | 0 | -1 |
|---|---|---|---|
| Appropriate comparison groups | Comparison groups have similar baseline characteristics | Minor differences exist between groups, or it is unclear if differences exist | Significant differences exist between groups |
| Follow up of subjects | Subject follow up was complete and thorough | Unable or unnecessary to complete follow up (mortality study) | Subject follow up was needed but not completed |
| Temporal relation | Exposure of interest precedes the outcome | Unclear if the exposure of interest precedes the outcome | Outcome proceeds the expected exposure period |
| Study results consistent with other available evidence | Study outcome is consistent with other available evidence | Outcome is partially consistent or no other evidence is available for comparison | Overall study outcome is not consistent with other available evidence |

**Table 13. Study quality and ROB scoring criteria for animal studies**

| Score Criteria | 1 | 0 | -1 |
|---|---|---|---|
| Multiple species | Studied examined effects in multiple species | Studied examined effects in a single species | Species not clearly stated |
| Both sexes | Studied examined effects in both sexes | Studied examined effects in a single sex | Sex not specified |
| Exposure regimes (repeated vs continuous) | Studied examined effects following different exposure regimes | Studied examined effects following a single exposure regime | Exposure regime not stated |
| Identical experimental conditions across study groups | Study used identical experimental methods across study groups | Minor differences exist, or it is unclear if identical experimental methods were used | Significant differences exist that could affect the outcome |
| Concentration relevant to human exposure | Study used a biologically and environmentally relevant exposure concentration | Unclear whether exposure concentration used was biologically and/or environmentally relevant | Exposure concentration was not biologically and/or environmentally relevant |
| Dose applicable to ReV development | Dose can be used directly to establish a POD for ReV development | Dose must be converted/calculated in order to establish a POD | Dose cannot be converted into an appropriate POD |
| Dose-response relationship | Critical effect showed a significant positive dose-response curve | Critical effect failed to show a significant dose-response curve | Critical effect showed a significant negative dose-response curve |

Rankings for each of the identified studies can be found in Table 14 (human studies) and Table 15 (animal studies). Note that total scores were added as a guide to compare within the study groups, but because each study group has a different number of scoring criteria, totals should not be compared across groups.

**Table 14. Study quality and ROB scoring for the selected DEA/TEA human studies**

| Study criteria | Henrik-Eckerman 2006 | Herman 1983 | Levin 1994 | Lillienberg 2008 | Piipari 1998 | Savonius 1994 | Yacher 2000 |
|---|---|---|---|---|---|---|---|
| **General** | | | | | | | |
| Original data | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Applicable route of exposure | 1 | -1 | 1 | 1 | 1 | 1 | 1 |
| Single route of exposure | -1 | -1 | 0 | 0 | 0 | 0 | 0 |
| Single chemical exposure | -1 | -1 | -1 | -1 | 1 | 0 | 0 |
| Range of doses/exposures | 1 | -1 | 0 | 0 | 1 | -1 | 0 |
| Exposure concentration known/ measured | 1 | -1 | 0 | 0 | 1 | -1 | 1 |
| Blinded study | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Health effects relevant to ReV development | -1 | -1 | -1 | -1 | 1 | 1 | -1 |
| Appropriate endpoints measured | -1 | -1 | 0 | 0 | 1 | 1 | -1 |
| Measured outcomes reported | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Study design sufficient/ clearly defined | 1 | -1 | 1 | 1 | 1 | 0 | 1 |
| Calculation of sample size | 0 | 0 | 0 | -1 | -1 | -1 | 0 |
| Confounding factors | -1 | -1 | -1 | -1 | 0 | 0 | 0 |
| Appropriate research practices | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| **Human** | | | | | | | |
| Appropriate comparison groups | 0 | 0 | 0 | 0 | -1 | 1 | 0 |
| Follow up of subjects | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Temporal relation | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| Study results consistent with other available evidence | 0 | 1 | 0 | 0 | 1 | 1 | 0 |
| **Total Points** | **1** | **-4** | **1** | **0** | **10** | **7** | **3** |
| **Study Selection – Key, supporting, or informative** | **I** | **I** | **I** | **I** | **S** | **S** | **I** |
| **Acute or chronic** | **A/C** | **A** | **A/C** | **A/C** | **A** | **A/C** | **A/C** |

**Table 15. Study quality and ROB scoring for the selected DEA/TEA animal studies**

| Study criteria | Gamer et al. (2008) | Gamer et al. (1996) | Gamer et al. (1993) |
|---|---|---|---|
| **General** | | | |
| Original data | 1 | 1 | 1 |
| Applicable route of exposure | 1 | 1 | 1 |
| Single route | 1 | 1 | 1 |
| Single chemical exposure | 1 | 1 | 1 |
| Range of doses/ exposures | 1 | 1 | 1 |
| Exposure concentration known/ measured | 1 | 1 | 1 |
| Blinded study | 0 | 0 | 0 |
| Health effects relevant to ReV development | 1 | 1 | 1 |
| Appropriate endpoints measured | 1 | 1 | 1 |
| Measured outcomes reported | 1 | 1 | 1 |
| Study design sufficient/ clearly defined | 1 | 1 | 1 |
| Calculation of sample size | -1 | -1 | -1 |
| Confounding factors | 1 | 1 | 1 |
| Appropriate research practices | 1 | 1 | 1 |
| **Animal** | | | |
| Multiple species | -1 | -1 | -1 |
| Both sexes | 1 | 1 | 0 |
| Exposure regimes (repeated vs continuous) | 1 | 1 | 1 |
| Concentration relevant to human exposure | 1 | 1 | 1 |
| Dose applicable to ReV development | 1 | 1 | 1 |
| Dose-response relationship | 1 | 1 | 1 |
| **Reproductive/developmental** | | | |
| Critical window for effects | 0 | 0 | 1 |
| Maternal and fetal toxicity | 0 | 0 | 1 |
| **Total Points** | **15** | **15** | **16** |
| **Study Selection – Key, supporting, or informative** | **K** | **S** | **S** |
| **Acute or chronic** | **A/C** | **C** | **A/C** |

## *A.5 Evidence Integration*

After addressing the study quality and ROB for each of the selected studies, the information from each of the data streams (human, animal, mechanistic) was compiled together and assessed for use as key, supporting, and informative studies. This information was put into the evidence integration tables found in Tables 16 and 17.

**Table 16. Evidence Integration Table for Human Studies**

| Study | Species | Type | Reasoning |
|---|---|---|---|
| Henriks-Eckerman et al. (2006) | Human | Informative | - Personal air sampling/measured air concentrations<br>- No measured health effects |
| Herman et al. (1983) | Human | Informative | - Examined sensitive population<br>- Exposure route unknown/possible multiple routes<br>- Single subject<br>- No exposure concentrations available |
| Levin et al. (1994) | Human | Informative | - Personal air sampling/measured air concentrations<br>- No measured health effects<br>- Exposed to a mixture |
| Lillienberg et al. (2008) | Human | Informative | - Measured air concentrations, but actual exposure unknown<br>- No measured health effects<br>- Exposed to a mixture |
| Piipari et al. (1998) | Human | Supporting | - Examined sensitive population<br>- Single subject<br>- Measured air concentrations<br>- Measured relevant health effects |
| Savonius et al. (1994) | Human | Supporting | - Examined sensitive population<br>- Possibly multiple routes of exposure<br>- No exposure concentrations available |
| Yacher et al. (2000) | Human | Informative | - Personal air sampling/measured air concentrations<br>- No measured health effects |

**Table 17. Evidence Integration Table for Selected Animal Studies**

| Study | Species | Type | Reasoning |
|---|---|---|---|
| Gamer et al. (2008) | Rats | Key | - Single species examined<br>- Examined both DEA and TEA<br>- Acute (5-d TEA) study<br>- Subacute range finding study<br>- Chronic (> 90-day) study<br>- NOAEL/LOAEL identified for DEA<br>- Similar critical effects for DEA and TEA |
| Gamer et al. (1996) | Rats | Supporting | - Single species examined<br>- Examined DEA<br>- Subchronic (90-day) study<br>- Higher-dose study than Gamer et al. (2008)<br>- Only free-standing LOAEL identified |
| Gamer et al. (1993) | Rats | Supporting | - Single species examined<br>- Examined DEA<br>- Gestational exposure study<br>- Developmental/reproductive various endpoints assessed<br>- NOAEL/LOAEL identified for maternal toxicity and fetotoxicity |

## *A.6 Confidence Rating*

Table 18 provides scoring criteria to rate the confidence and uncertainty for each aspect or element of the toxicity assessment. The table provides the name of the element and the magnitude of the confidence in each element using a qualitative ranking system of low, medium, or high confidence. Table 19 displays the overall confidence in the DEA and TEA toxicity assessment.

**Table 18. Confidence Scoring Criteria**

| Element | Low | Medium | High |
|---|---|---|---|
| Database Completeness | A single acute and/or chronic study was available | Several studies were available, but some important studies were missing. | Two studies in different species, one 2-generation reproductive study, two developmental studies |
| Systematic Review | A systematic approach was not used. | A systematic approach was considered and some criteria were applied, but a full review was not conducted | A systematic approach was used in study evaluation and clear criteria are established for judgment |
| Key Study Quality | Selected study has deficiencies, but is still considered useful | Selected study was reasonably well done but some restrictions must be considered | Selected study was well done and can be used without restriction |
| Critical effect | Critical effect or dose-response curve was moderate to severe. MOA information not available. | Critical effect was moderate; other studies are deemed necessary to determine the critical effect. | Critical effect was of minimal, or the confidence in the critical effect was high. MOA information available. |
| Relevance of Critical Effect | Critical effect identified in animal studies is only assumed to be relevant to humans; MOA is not known for the critical effect | Critical effect appears to be relevant to humans. MOA is known for the critical effect and possibly relevant to humans. | Critical effect based on a human study or matches observed human experience; MOA is well understood so critical effect is assumed relevant. |
| Point of Departure (POD) | Many uncertainties exist in POD; only a free-standing NOAEL or LOAEL identified; few dose groups; BMD modeling not possible | Some uncertainty exists in POD, NOAEL or LOAEL; few dose groups; difference between BMD and BMDL is large | Basis for POD well understood: NOAEL and LOAEL; multiple dose groups, BMD modeling conducted; difference between BMD and BMDL less than 2-fold |
| Human Equivalent POD ($POD_{HEC}$) | Many uncertainties exist in the PODHEC; no dosimetric adjustment from animal POD to PODHEC | Default adjustments used and considered conservative; some uncertainty exists in adjustment to a HEC. | Human data available; HED/HEC is known from PBPK or dosimetry model or CSAF |
| Sensitive Populations | Many uncertainties on sensitive populations exist and are not addressed. | Information on sensitive population is not known but default procedures are presumed to be conservative. | Human data on sensitive populations are available and uncertainties are addressed. |
| Peer Review | Limited or no peer review; disregarded comments would significantly change risk value; no independent check | Adequate peer review. Most substantive comments addressed; disregarded comments would not significantly change value | High quality panel peer review with appropriate experts; all substantive comments addressed as per independent check |
| Toxicity Value Comparison | Relevant risk values show a greater than 10 fold difference. | Some relevant risk values agree within 3-fold of each other, and others disagree within 10-fold of each other | All relevant risk values agree within 3-fold of each other |

**Table 19. Confidence in the Toxicity Assessment**

| Element | Score | Basis |
|---|---|---|
| Database Completeness | Medium | - Several human and occupational studies but lacked PODs<br>- Three well-conducted animal studies using DEA and/or TEA<br>- Several oral reproductive and developmental studies<br>- Lacking a 2-generation reproductive study and a detailed acute study |
| Systematic Review | High | - Systematic review conducted |
| Key Study Quality | Medium | - Acute portion considered low, range-finding study, fewer animals and dose groups, and did not histopathologically examine the target tissue<br>- Chronic portion considered high, well-conducted study using both DEA and TEA with multiple doses and endpoints |
| Critical effect | Medium | - Acute and chronic critical effects were mild and potential critical effects similar<br>- DEA and TEA caused similar critical effects |
| Relevance of Critical Effect | Medium | - Acute and chronic critical effects are possibly relevant to humans<br>- Available human studies suggest POE effects |
| Point of Departure (POD) | Low | - Acute and chronic NOAELs and LOAELs available, BMD modeling conducted for the chronic ReV<br>- Acute considered medium, chronic considered high |
| Human Equivalent POD ($POD_{HEC}$) | Medium | - Default adjustments used, considered conservative<br>- MPPD modeling used for animal-to-human dosimetric adjustments |
| Sensitive Populations | Medium | - Default $UF_H$ of 10 used and considered protective<br>- Acute ReV ~4 times lower than concentration resulting in respiratory effects in a DEA-sensitized subject |
| Peer Review | High | - DSD will be proposed for public comment and the chronic ReV underwent external peer review as part of the scientific publication process |
| Toxicity Value Comparison | - | - OEHHA chronic REL 3 µg/$m^3$ is within an order of magnitude of the chronic ReV; however, neither the DEA low-dose study nor critical recent guidance regarding the adversity of rodent laryngeal lesions were available for consideration in the OEHHA evaluation |

| Confidence Scoring Summary | | | |
|---|---|---|---|
| **Not Evaluated** | **Low Confidence** | **Medium Confidence** | **High Confidence** |
| Peer Review – Acute ReV | | Database Completeness<br>Key Study Quality<br>Relevance of Critical Effect<br>Point of Departure<br>Human Equivalent POD<br>Sensitive Populations<br>Toxicity Value Comparison | Systematic Review<br>Critical Effect<br>Peer Review – Chronic ReV |

* Criteria for scoring the individual elements adapted from Beck et al. (2015).

# Appendix 2 Estimating Tidal Volume and Breathing Frequency Values for Input into the MPPD Model

The default minute ventilation (VE) used by the MPPD model for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values, which correspond to the default USEPA minute ventilation. However, they are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. de Winter-Sorkina and Cassee (2002) calculated tidal volume and breathing frequency values corresponding to various minute ventilation values for use in the MPPD model. Therefore, the TD used human tidal volume and breathing frequency data from Table 2 of de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation (13,800 mL/min) for input into the MPPD model (data reproduced in Table 15). More specifically, the TD used data for exertion levels of rest through heavy (see below), below the switch to oronasal (mouth and nose) breathing around a minute ventilation of 35 L/minute, as the USEPA (1994) default of 13.8 L/minute falls within this range and is associated with nasal breathing.

**Table 20. Human Tidal Volume and Breathing Frequency Data[a]**

| Breathing Frequency (breaths/min) | Tidal Volume (mL) | Associated Minute Ventilation (L/min) | Exertion Level |
|---|---|---|---|
| 10 | 500 | 5 | Rest |
| 12 | 625 | 7.5 | Rest |
| 16 | 813 | 13.0 | Light |
| 19 | 1000 | 19.0 | Light |
| 22 | 1136 | 25.0 | Light |
| 24 | 1250 | 30.0 | Modest |
| 26 | 1346 | 35.0 | Modest |
| 28 | 1429 | 40.0 | Modest |
| 34 | 1735 | 59.0 | Heavy |

[a] from Table 2 of de Winter-Sorkina and Cassee (2002)
http://rivm.openrepository.com/rivm/bitstream/10029/9272/1/650010031.pdf

Based on values represented in the 2002 paper, tidal volume and breathing frequency are highly linearly related ($R^2$ = 0.9988), with breathing frequency (breaths/min) multiplied by 51.465 being approximately equal to tidal volume (mL/breath) (see graph below). As the relationship is linear, this process is very similar to interpolation.

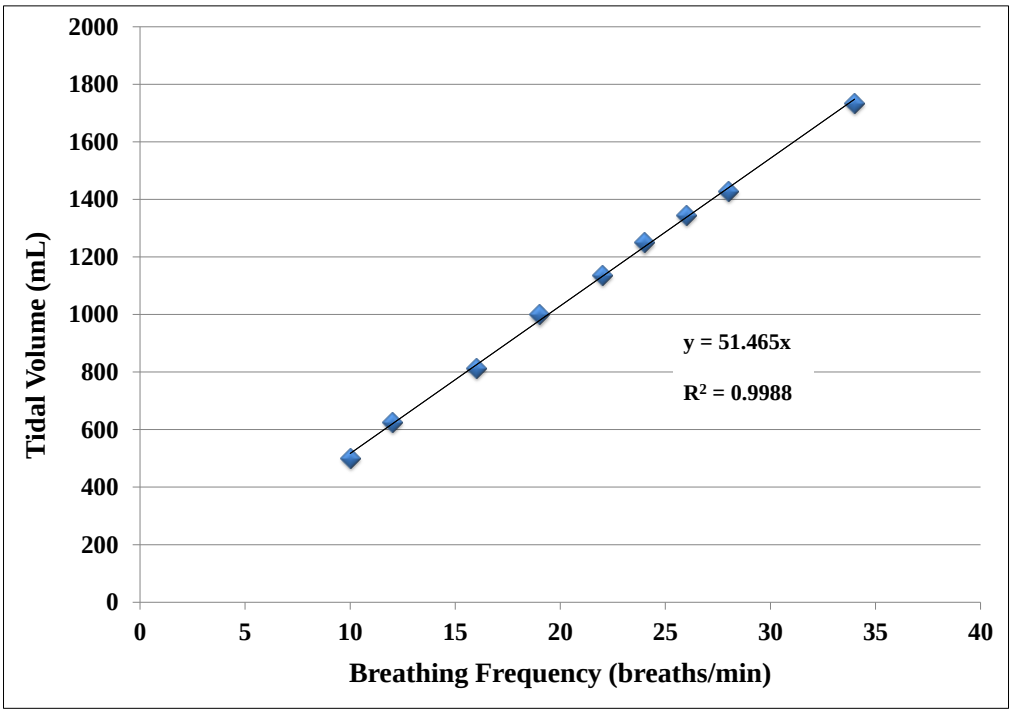



**Figure 1. Relationship Between Human Tidal Volume and Breathing Frequency**

Based on the above linear relationship between tidal volume and breathing frequency, because minute ventilation (mL/min) equals tidal volume (mL/breath) multiplied by breathing frequency (breaths/min), the breathing frequency and tidal volume associated with a desired minute ventilation within this range (< 35,300 mL/minute) may be calculated as follows:

(1) minute ventilation (mL/min) = tidal volume (mL/breath) * breathing frequency (breaths/min)

(2) From the equation of the line in the graph above (y=51.465x), tidal volume (y-axis) equals 51.465x and breathing frequency (x-axis) equals x, so multiplying them together per equation (1) yields a product of $51.465x^2$. Substituting this value into the equation for "tidal volume * breathing frequency"

minute ventilation = tidal volume * breathing frequency = $51.465x^2$

(3) Solving the above equation 2 "minute ventilation = $51.465x^2$" for x (breathing frequency)

breathing frequency (breaths/min) = (minute ventilation)$^{0.5}$ / $(51.465)^{0.5}$

(4) Tidal volume may then be calculated

tidal volume (mL/breath) = 51.465 * breathing frequency (calculated using equation 3 above)

Using the default USEPA (1994) human minute ventilation value (13,800 mL/min), the associated breathing frequency and tidal volume may be calculated from equations 3 and 4 above:

**breathing frequency (breaths/min)** = (minute ventilation)$^{0.5}$ / $(51.465)^{0.5}$

= $13{,}800^{0.5}$ / $(51.465)^{0.5}$

= 117.4734 / 7.173911

= 16.375 breaths/min

**tidal volume (mL/breath)** = 51.465 * breathing frequency

= 51.465 * 16.375

= 842.74 mL/breath

[confirmation calculation: minute ventilation (mL/min) = tidal volume (mL/breath) * breathing frequency (breaths/min) = 842.74 mL/breath * 16.375 breaths/min = 13,800 mL/min = USEPA default]

# Appendix 3 Acute Animal-to-Human Dosimetric Adjustments (MPPD Model)

In the key study, an aerosol of DEA was used. The Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research and National Institute for Public Health and the Environment (RIVM) 2004 multiple path particle dosimetry model (MPPD) v 3.0 program (CIIT and RIVM 2004; Asgharian et al. 2014) was used to calculate the deposition fraction of DEA in the target respiratory region. Parameters necessary for this program are particle diameter (MMAD = 1.1), standard deviation (GSD = 3), particle density (unknown, default value of 1 g/cm3) and pulmonary regions considered. The target region for DEA was considered to be the total particle distribution in the larynx (head region). Once the total particle distribution was determined, the RDDR was calculated (Section 3.1.4.2).

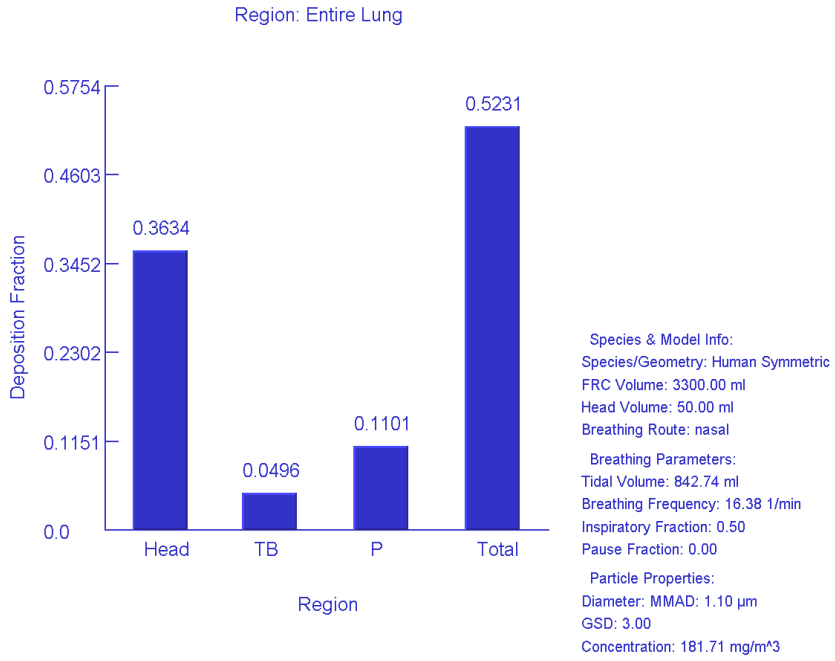



**Figure 2. Human MPPD modeling results**

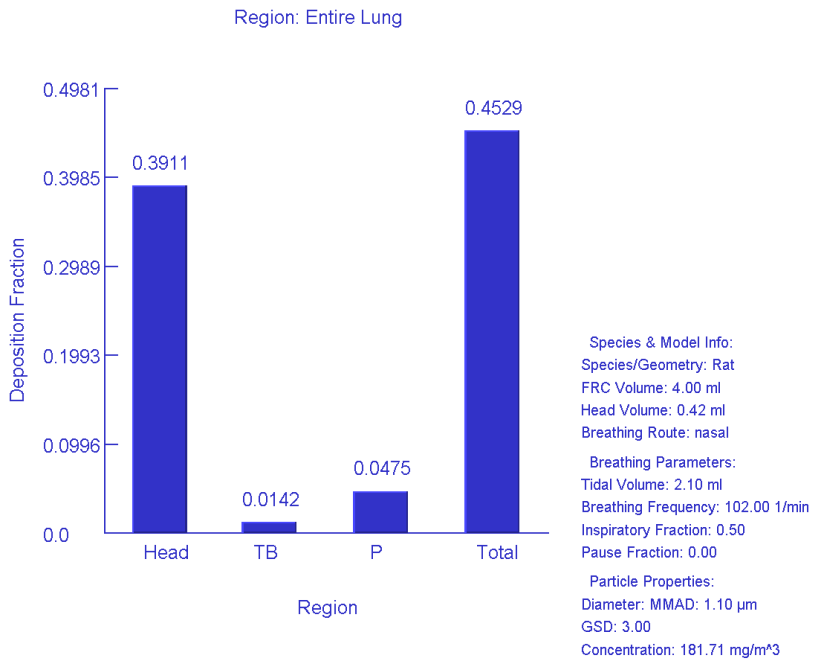



**Figure 3. Rat MPPD Modeling Results**