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Diethylamine

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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
°C	degrees Celsius
BMR	benchmark response
BW	body weight
CNS	central nervous system
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
EPI	epithelium
GSD	geometric standard deviation (σ_g)
h	hour(s)

Acronyms and Abbreviations	Definition
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute(s)
MMAD	mean mass aerodynamic diameter
MOA	mode of action
n	number
NAV	nasal airway volume
NAR	nasal airway resistance
nd	not determined
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OSHA	Occupational Safety and Health Administration
pKa	Acid dissociation constant

Acronyms and Abbreviations	Definition
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
RDDR	regional deposited dose ratio
ReV	reference value
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
USEPA	United States Environmental Protection Agency
VE	minute volume
VE_h	default non-occupational ventilation rate for a 24-h day (20 m^3/day)
wk	week(s)

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 evaluation of diethylamine (DEA). Please refer to Section

1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on DEA's physical/chemical data.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV	**Short-Term Health** **330 µg/m^3 (110 ppb)**	**Critical Effect**: Nasal and eye sensory irritation in humans
$^{acute}ESL_{odor}$	**Odor** **180 µg/m^3 (60 ppb)**	Characteristic fishy, ammonia-like odor
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**Long-Term Health** **33 µg/m^3 (11 ppb)**	**Critical Effect(s)**: Hyperostosis in the turbinates in mice
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	No evidence of carcinogenic activity via the inhalation route
$^{chronic}ESL_{veg}$	- - -	No data found

[a] DEA is not monitored for by the TCEQ's ambient air monitoring program

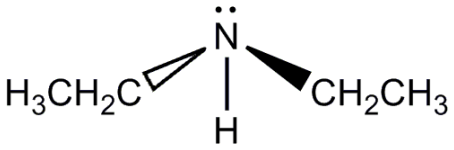
Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	**Concentration**	**Notes**
^{acute}ESL [1 h] (HQ = 0.3)	**Short-Term ESL for Air Permit Reviews 99 µg/m^3 (33 ppb) [a]**	**Critical Effect**: Nasal and eye sensory irritation in humans
^{acute}ESL$_{odor}$	**180 µg/m^3 (60 ppb)**	Characteristic fishy, ammonia-like odor
^{acute}ESL$_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	**Long-Term ESL for Air Permit Reviews [b] 9.9 µg/m^3 (3.3 ppb)**	**Critical Effect(s)**: Hyperostosis in the turbinates in mice
^{chronic}ESL$_{nonthreshold(c)}$ ^{chronic}ESL$_{threshold(c)}$	- - -	No evidence of carcinogenic activity via the inhalation route
^{chronic}ESL$_{veg}$	- - -	No data found

[a] Based on the acute ReV of 330 µg/m^3 (110 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[b] Based on the chronic ReV of 33 µg/m^3 (11 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

Table 3 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_4H_{11}N$	HSDB (2015) [a]
Chemical Structure		NTP 2011
Molecular Weight ($gmol^{-1}$)	73.1	NIOSH (2011) [b]
Physical State at 25°C	Liquid	NIOSH (2011) [b]
Color	Colorless	NIOSH (2011) [b]
Odor	Fishy, ammonia-like odor	NIOSH (2011) [b]
CAS Registry Number	109-89-7	NIOSH (2011) [b]
Synonyms	Diethamine; N,N-diethylamine; ethanamine, N-ethyl; N-ethylethanamine	HSDB (2015)
Solubility in water	Miscible	NIOSH (2011) [b]
Log Kow	0.58	HSDB (2015) [a]
pKa	11.09 at 20 °C	HSDB (2015) [a]
Density (water = 1)	0.71	NIOSH (2011) [b]
Vapor Pressure	192 mm Hg	NIOSH (2011) [b]
Melting Point	-50 °C	HSDB (2015) [a]
Boiling Point	132°F	NIOSH (2011) [b]
Conversion Factors	1 ppm = 2.99 mg/m^3; 1 mg/m^3 = 0.33 ppm	NIOSH (2011) [b]

[a] accessed on June 15, 2015.

[b] accessed on July 6, 2014.

Chapter 2. Major Sources and Uses

DEA is used as an organic intermediate in industry to produce the corrosion inhibitor, N, N-diethylethanolamine. It is widely used in rubber, pharmaceuticals, resins, pesticides, insect repellants, and dye processing. In addition, DEA can be used as a polymerization inhibitor (ACGIH 2001; NTP 2011). DEA is a high production volume (HPV) chemical and has ubiquitous occurrence in trace amounts (NTP 2011). Neurath et al. (1977) and Uhegbu and Maduagwu (1995) reported that DEA occurs naturally in foods and plants. According to Grant (1986), DEA is produced during decay of fish.

According to the information submitted to the USEPA by companies for chemicals under the 1989-2002 inventory update rule (IUR), U.S. production of DEA ranged from 10 – 50 million pounds (40 CFR part 710 subpart B; 51FR21438 (HSDB 2015)).

DEA is not monitored for by the TCEQ's ambient air monitoring program, so currently no ambient air data (i.e., peaks, annual averages, trends, etc.) are available. Key et al. (2011) developed an analytical method to measure trace nitrogenous atmospheric bases. The concentration of DEA measured in ambient air in Hermon Park (Los Angeles, CA, USA) ranged from nondetected to 28 part per trillion by volume DEA (sampled for three-hour (h) periods between 4 and 7 pm over the course of five days in September 2009).

Chapter 3. Acute Evaluation

NTP (2011) and Montelius (2013) recently reviewed the toxicity of DEA. The TCEQ reviewed the toxicity information in these documents, and also conducted a thorough review of the literature since 2008.

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

DEA is a respiratory irritant whose effects occur primarily in the upper respiratory tract. It is also an eye irritant to humans (Lundqvist et al., 1992). The acute toxicity of DEA has been investigated in various animal species by a variety of exposure methods. In a few animal studies, systemic effects were not noted except at high concentrations (NTP 2011). Exposure to DEA can be through inhalation, ingestion, or dermal route. When in contact with the eyes and nose, DEA can lead to sensory irritation (Mackison et al. 1981).

3.1.1 Physical/Chemical Properties

DEA is a colorless liquid at room temperature with a fishy, ammonia-like odor (ACGIH 2001; NIOSH 2011). It has a molecular weight of 73.1 g mol^{-1} and is highly flammable with a vapor pressure of 192 mm Hg at 20ºC (NIOSH 2011). DEA is highly water soluble. As reported in HSDB (2015), DEA is soluble in alcohol, ether, carbon tetrachloride, chloroform, paraffin

hydrocarbons, aromatic and aliphatic hydrocarbons, fixed oils, mineral oils, and oleic and stearic acids. It has a K_{ow} of 0.58 (HSDB 2015). Other physical/chemical properties of DEA can be found in Table 3 above.

3.1.2 Human Studies

According to NIOSH (2011), short-term inhalation exposure of occupational workers to DEA can cause initial corrosive effects on eyes and/or airways. Lung edema and pneumonitis may then occur. Severe swelling of the throat may occur after exposure at high levels.

3.1.2.1 Key Human Study (Lundqvist et al. 1992)

Lundqvist et al. (1992) used seven healthy nonsmoking subjects (1 female and 6 males) to investigate DEA exposure under two separate exposure scenarios.

For the first study, four healthy nonsmoking adult individuals were exposed to 25 ppm (75 mg/m^3) DEA for 15 minutes (min) in a climate chamber. The sex of these four individuals was not provided. Nasal volume and resistance were measured by acoustic rhinometry and rhinomanometry. Nasal irritation (which was expressed by swelling measured with acoustic rhinometry) and air flow in the nose (with the aid of pneumotachometer) were measured.

Acute change in nasal airway volume (NAV), usually seen as acute nasal mucosal response to thermal stimuli, was not observed in the test subjects at 25 ppm (75 mg/m^3), which is higher than the current TLV-STEL value of 15 ppm (45 mg/m^3) (ACGIH 2001). NAV measurement did not reveal acute reaction to DEA in the measurement series during the 15-min exposure to 25 ppm (75 mg/m^3). Also, there was no acute change in nasal airway resistance (NAR). The overall mean NAR showed a slight decrease after exposure (average before: 2.38; average after: 2.13); however, according to the authors, this change was not significant ($p > 0.1$). For acute nasal reactions, statistical analysis was carried out using the Mann – Whitney rank sum test. Each individual had multiple measurements taken before exposure, during exposure, and after exposure. According to Lundqvist et al. (1992), this approach is useful in comparing means of nasal volume values in the exposure and the post-exposure periods with those of the pre-exposure periods. In this study, the free standing NOAEL for nasal response was 25 ppm.

A subsequent part of the Lundqvist et al. (1992) study was aimed at determining acute sensory effects in five healthy, non-smoking adult males, exposed to concentrations of DEA (in increasing order from 0 to 12 ppm) for 60 min. Subjective sensations, which include perceived odor intensity and sensory irritation, termed specifically as eye and nasal irritation, were registered on linear visual analogue scales attached to a questionnaire. Subjects were asked to allocate marks (based on what they sensed) on the scale, immediately after entrance into the study chamber and every 5 minutes until just before exiting the chamber. For acute sensory

effects, the study made use of correlation analyses of data on sensory irritation and odor perception by employing the use of PC Statistical Program.

The second study showed moderate to strong olfactory responses and distinct nasal and eye irritation in the test subjects exposed to DEA vapor, at an average of 10 ppm exposure concentration for 60 min. Subjective responses pertaining to odor perception, nose and eye irritation, showed large variations in individual sensitivity and tolerance when simultaneously read. There was also a five- to six-fold difference (among the test subjects) in visual analogue scaling points both at the start and at the end of the study. The results further showed significant correlations between nose irritation and eye irritation scaling ($r = 0.87$; $p < 0.001$) and between nose irritation and odor perception ($r= 0.71$; $p < 0.001$).

Nasal irritation after a 60-min exposure to DEA (average 10 ppm) ranged from 2-6 on the response intensity scale while eye irritation after the 60-min exposure ranged from 1-5 on the response intensity scale. The reactions can be classified as mild to moderate responses. Based on the results from this study the eye is likely to be more sensitive to DEA than the nose. In this study, the minimal to moderate LOAEL for eye and nasal irritation was 10 ppm.

According to the study, employing the use of NAV and NAR changes as bioassay for neurogenic sensory irritation was not found to be applicable at the exposure levels. Lundvquist et al. (1992) further states that an increase in the DEA exposure duration is unlikely to increase its odor perception as well as trigeminal irritation reflexes, which occur within a time scale of seconds to minutes (Nielson 1991). In other words, irritation was concentration-dependent.

3.1.2.2 Supporting Human Studies

One case of double vision was reported in an employee handling DEA, but further details were not provided (Munn 1967; cited by BASF 1995). In an unrelated report by Grant (1986; cited by BASF, 1995), double vision from occupational exposure to DEA was recorded. The symptoms became apparent several hours after exposure. When workers were occupationally exposed to low concentrations (not provided), the symptoms disappeared after 1 day. At higher DEA exposure concentrations (not provided), the symptoms persisted for numerous days.

3.1.3 Animal Studies

High-quality animal studies were conducted by NTP (2011), which produced the lowest NOAEL and LOAEL values. The following sections focus on NTP (2011), but Table 6 provides a summary of pertinent acute and subacute inhalation studies arranged from effects that occur at the lowest concentrations upward. Appendix A (reproduced from NTP 2011) provides additional information on these acute/subacute inhalation studies.

3.1.3.1 Key Animal Studies (NTP 2011)

The National Toxicology Program (NTP) (2011) provided reports of an acute two-week toxicity study of DEA in rats and mice (F344/N rats and B6C3F1 mice). The details of the study are summarized in the following sections.

3.1.3.1.1 Two-Week Study in Rats (NTP 2011)

Groups of five male and five female rats were exposed to DEA vapor at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 hours (h) per day (h/d), 5 day per week (d/wk) for 16 days. Concentrations were analytical determined.

All rats survived to the end of the study. The mean body weights of the 250 and 500 ppm exposure groups for males and females, and 125 ppm exposure group for males were significantly less than those of the chamber controls. In the male and female rats, there were no significant body weight changes between the control and test animals in the 31 and 62.5 ppm exposure groups, or the 125 ppm test group for female rats.

Suppurative inflammation of the cornea was present in most rats exposed to 500 ppm. Focal eye lesions were noted at necropsy in four males and three females exposed to 500 ppm and one male exposed to 250 ppm. Crusty noses were observed in most 500 ppm exposed males and females and in two 250 ppm exposed males. The thymus weights of males exposed to 125 ppm or greater and females exposed to 500 ppm were significantly less than those of the chamber controls.

All rats at 500 ppm developed ulcers in the respiratory epithelium (EPI). There was atrophy of the olfactory EPI in all rats exposed to 250 or 500 ppm. Ulcer of the nasopharyngeal duct was present in all 500 ppm exposed rats. Suppurative inflammation, necrosis of the turbinates (except in one female exposed at 125 ppm), and squamous metaplasia of the respiratory EPI of the nose were present in all rats exposed to 125 ppm or greater. Minimal responses, namely suppurative inflammation (in 5 males and 2 females), ulcer of the respiratory EPI (in 1 male rat), metaplasia (of squamous cells) of the respiratory EPI (in 5 males and 2 females), were observed in the 62.5 ppm DEA exposure group. There was no sensory irritation or cellular damages in the 31 ppm exposure group. Table 4 shows the nasal lesions that occurred at the lowest concentrations that had increasing severity grades. Male rats were slightly more sensitive than female rats.

Therefore, in the rats, 31 ppm is the NOAEL and 62.5 ppm the LOAEL, with the critical effects being suppurative inflammation and respiratory EPI (metaplasia, squamous).

Table 4 Histological Assessment of Noses of Rats for the 2-Week Study – Critical Effects

Nonneoplastic Lesion	Sex	0 ppm (5 M, 5 F)	31 ppm (5 M, 5 F)	62.5 ppm (5 M, 5 F)	125 ppm (5 M, 5 F)	250 ppm (5 M, 5 F)	500 ppm (5 M, 5 F)
Inflammation, Suppurative	M	0	0	5 [a] ** (1.6) [b]	5 ** (2.8)	5 ** (3.8)	5 ** (4.0)
Inflammation, Suppurative	F	0	0	2 (1.0)	5 ** (2.2)	5 ** (3.8)	5 ** (4.0)
Turbinates, Necrosis	M	0	0	0	5 ** (2.2)	5 ** (3.8)	5 ** (3.4)
Turbinates, Necrosis	F	0	0	0	4 * (2.0)	5 ** (3.0)	5 ** (3.8)
Respiratory EPI, metaplasia, squamous	M	0	0	5 ** (1.0)	5 ** (2.2)	5 ** (3.0)	5 ** (3.0)
Respiratory EPI, metaplasia, squamous	F	0	0	2 (1.0)	5 ** (2.2)	5 ** (2.8)	5 ** (3.0)

[a] Number of animals with lesions

[b] Average severity grade of lesions in affected animals in parentheses: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

* $P < 0.05$

** $P < 0.01$

3.1.3.1.2 Two-Week Study in Mice (NTP 2011)

Groups of five male and five female mice were exposed to DEA vapor at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 h/d, 5 d/wk for 17 days. Analytical method of measuring exposure concentration was employed in this study (NTP 2011).

At 500 ppm, two males and 3 females died in the first week. All mice exposed to 250 and 500 ppm lost weight during the course of the study. Final mean weight and mean body weight gains in all mice exposed to 125 ppm or greater were significantly less than those of the controls. At exposure to 31 and 62.5 ppm, no significant changes in body weight were observed between the male control and test groups. However, in females, no significant changes in body weight were observed between the control and test groups at exposure to 31, 62.5 and 125 ppm DEA. Males were generally more sensitive than females.

Lethargy, abnormal breathing, and thinness were observed in most mice exposed to 250 or 500 ppm. Eye irritation and discharge, nasal discharge, and low fecal and urine output were noted in 500 ppm exposed mice. Thymus weights of the 250 and 500 ppm exposed males and 125 ppm or greater exposed females were significantly less than those of the chamber controls.

In the lung, the incidence of minimal chronic active inflammation of main-stem bronchi was significantly increased in 500 ppm exposed males. Suppurative inflammation of the nose occurred in all males exposed to 250 or 500 ppm and all females exposed to 125 ppm or greater, and most males exposed to 125 ppm. Squamous metaplasia of the respiratory EPI and olfactory epithelial atrophy were seen in mice exposed to 125 ppm or greater, although there was not a strong increase in severity grades. Turbinate necrosis occurred in all exposed mice except one female in the 31 ppm exposure group (strong increase in severity response (Table 5)). Therefore, the critical effect is necrosis in the turbinates with a LOAEL of 31 ppm (Table 5). For nasal responses, there were minimal differences between male mice and female mice.

Table 5 Histological Assessment of Noses of Mice for the 2-Week Study – Critical Effect

Nonneoplastic Lesion	Sex	0 ppm (5 M, 5 F)	31 ppm (5 M, 5 F)	62.5 ppm (5 M, 5 F)	125 ppm (5 M, 5 F)	250 ppm (5 M, 5 F)	500 ppm (5 M, 5 F)
Turbinates, Necrosis	M	0	5 ** [a] (1.0) [b]	5 ** (1.0)	5 ** (1.8)	5 ** (3.8)	5 ** (3.6)
Turbinates, Necrosis	F	0	4 * (1.0)	5 ** (1.0)	5 ** (2.2)	5 ** (3.4)	5 ** (3.8)

[a] Number of animals with lesions

[b] Average severity grade of lesions in affected animals in parentheses: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

* $P < 0.05$

** $P < 0.01$

3.1.3.2 Reproductive/Developmental Studies

Short-term reproductive/developmental studies have not been conducted for DEA. The alkyl amine class of compounds has generally not been shown to have reproductive/developmental effects except at doses/concentrations where maternal toxicity occurs (OECD 2011, 2013). However a 3-month inhalation study conducted by NTP (2011) evaluated reproductive tissues and estrous cycle characterization in both male and female rats and mice. Please refer to Section 4.1.2.2 for additional details. No effects on reproductive function were observed, except there was a dose-dependent decrease in sperm motility, but effects occurred at higher concentrations than adverse upper respiratory tract effects (Section 4.1.4). The findings from the 3-month study may not be applicable to a short-term 1-h inhalation exposure.

3.1.3.3 Sensitization Potential

There is some evidence that DEA may be a weak dermal sensitizer Montelius (2013), although other studies did not indicate DEA was a skin sensitizer. Refer to Montelius (2013) for additional

information. Appendix A provides a description of a two-stage sensitization test using female CF1 (BR) albino mice conducted by USEPA (1987) that demonstrated no sensitization potential. There is no evidence that DEA causes sensitization via inhalation exposure.

3.1.3.4 Summary of Acute Inhalation Studies

In rats, the concentration resulting in mortality in 50% of animals (LC_{50}) was reported as 4,000 ppm for a 4-h inhalation exposure (Smyth et al. 1951 as cited in NTP 2011). Male OF1 mice experienced expiratory bradypnea indicative of upper airway irritation after acute inhalation exposure (60 to 600 ppm for 15 min). The calculated concentration resulting in a 50% decrease in respiratory rate (RD_{50}) in mice was 202 ppm (Gagnaire et al. 1989 as cited in NTP 2011). Nielsen and Yamagiwa (1989), using male Ssc:CF-1 mice, reported an RD_{50} of 184 ppm (indicative of upper respiratory sensory irritation). In tracheal-cannulated mice, an RD_{50} of 549 ppm (indicative of pulmonary sensory irritation) was reported.

Table 6 provides a summary of the key acute human study (Lundqvist et al. 1992) and other acute and subacute animal studies (Union Carbide 1950; NIOSH 1984, 1987; and Lynch et al. 1986 as reported by NTP 2011) (summarized in Appendix A).

Table 6 Acute and Sub-Acute Inhalation Studies

Exposure Concentration (Species)	Exposure (Number/sex/dose)	NOAEL	LOAEL	Notes (References)
10 ppm average (Human) [a]	0-12 ppm (increasing) for 60 min (4 M and 1 F)	---	10 ppm	Nose and eye irritation (Lundqvist et al. 1992)
25 ppm (Human)	15 min (4 adults)	25 ppm Free-standing	---	Nasal neurogenic response (indicated by NAV and NAR) (Lundqvist et al. 1992)
0, 31, 62.5, 125, 250, or 500 ppm (B6C3F1 Mice) [b]	6 h/d, 5 d/wk for 17 days (5 M, 5 F)	---	31 ppm	Turbinates, necrosis of the nose at 31 ppm. Atrophy of olfactory EPI at 62.5 ppm (1 female mouse) (NTP 2011)
0, 31, 62.5, 125, 250, or 500 ppm (F344/N Rats)	6 h/d, 5 d/wk for 16 days (5 M, 5 F)	31 ppm	62.5 ppm	Suppurative inflammation; ulcer of the respiratory EPI in 1 male, squamous cell metaplasia of the respiratory EPI (NTP 2011)
25 or 250 ppm (Fisher 344 rats)	2 wk, 6.5 h/d, 5 d/wk (M, F)	25 ppm	250 ppm	Decreased body weight gain; sneezing, tearing, and reddened noses; histopathology not conducted at 2 wks (Lynch et al. 1986)
500 ppm (Fischer 344 rats)	10 days, 6 h/d, 5 d/wk (M, F)	---	500 ppm	Moderate to marked necrotizing inflammation in the nasal mucosa (NIOSH 1984 as cited in NTP 2011; Virginia Chemicals. 1987)
250 or 1,000 ppm (B6C3F1 mice)	16 d 6 h/d, 5 d/wk (M, F)	---	250 ppm	Acute ulcerative necrotizing rhinitis and squamous metaplasia of the nasal mucosa in all mice, with turbinate atrophy in some animals (NIOSH 1987 as cited in NTP 2011)
250 or 1,000 ppm (F344/N rats)	16 d 6 h/d, 5 d/wk (M, F)	---	250 ppm Acute peribronchiolar pneumonia in one rat	Squamous metaplasia of tracheal mucosa. Acute peribronchiolar pneumonia in several rats (NIOSH 1987 as cited in NTP 2011)
1,000, 2,000, 4,000, and 8,000 ppm (rats)	4 h 6 rats	1000 ppm dose well tolerated	2,000 ppm death in 1/6 rats	4,000 ppm, 3/6 deaths; eye and nose irritation, poor coordination. 8,000 ppm, 6/6 death; convulsion, bloody discharge from the nostrils, irritation of ears and feet to the point of rawness (Union Carbide 1950 as cited in NTP 2011)

[a] Key Human Study
[b] Key Animal Study: mice were the most sensitive species

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

DEA is strongly alkaline, with an acid dissociation constant (pKa) of 11.09 (HSDB 2015). It can cause cellular damage at high concentrations (refer to Section 4.1.3), although at lower concentrations sensory irritation occurs. Nielsen and Yamagiwa (1989) demonstrated sensory irritation effects are an important part of the odor sensation. The range of 50% odor detection thresholds is 20-50 ppb (Section 3.2.1).

Although the exact MOA for sensory irritation for DEA is not known, it is believed to cause sensory irritation involving two areas. The first is sensory irritation affecting the upper airways, resulting from the activation of trigeminal nerve endings in the nasal mucosa and causing burning and painful sensations. Pulmonary irritation occurs at higher concentrations, which affect the lower airways, resulting from vagal nerve ending stimulation and evoking a sensation of dyspnea and breathlessness (Nielsen & Bakbo 1985; Alarie and Stokinger 1973; Nielsen and Yamagiwa 1989). As mentioned previously, Nielsen and Yamagiwa (1989) reported an RD_{50} of 184 ppm for upper respiratory sensory irritation, whereas the RD_{50} for pulmonary sensory irritation was 549 ppm. These researchers concluded that DEA directly interacted with the trigeminal and vagal nerves. Therefore, the exposure concentration of the parent compound was used as the dose metric.

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

Since DEA causes mild sensory irritation in humans at 10 ppm, the minimal LOAEL of 10 ppm is chosen from the study by Lundqvist et al. (1992) for developing an acute ReV. The critical effects are eye and nasal irritation. Animal studies carried out by the NTP (2011) reported minimal cellular damage at higher concentrations (31 – 62.5 ppm) of DEA after a 2-wk exposure. The POD_{HEC}, based on a minimal LOAEL derived from the NTP (2011) animal study in mice, is 56.33 ppm (Appendix B), which is 5-6 times higher than the minimal LOAEL of 10 ppm derived from the human study.

3.1.6 Dosimetric Adjustments

The key study was conducted in humans, so an animal-to-human dosimetric adjustment is not needed. A dosimetric adjustment for exposure duration was not needed since the study exposure duration was for an average of 1 h, which is equivalent to the TCEQ's acute exposure duration. In addition, mild sensory irritation is assumed to be concentration dependent.

3.1.7 Adjustment of the POD_{HEC} and Application of Uncertainty Factors

The POD_{HEC} of 10 ppm was based on the human study by Lundqvist et al. (1992). Irritation in eye and nasal mucosa is assumed to have a threshold. The default for threshold effects is to determine a POD and apply uncertainty factors (UFs) to derive a reference value (ReV). The

following uncertainty factors (UFs) were applied to the POD_{HEC} of 10 ppm; 10 for intraspecies variability (UF_H), 3 for the LOAEL uncertainty factor (UF_L) and 3 for the database uncertainty factor (UF_D), for a total UF = 90.

- A UF_H of 10 was used to account for variation in sensitivity among the members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences.
- A UF_L of 3 was used because the critical effect is low to moderate, as nasal irritation intensity ranged from 2-6 while eye irritation intensity ranged from 1-5.
- A UF_D of 3 was used because the human study conducted by Lundqvist et al. (1992) only made use of 5 subjects. In addition to this, the study design was not blind, although this might bias the study results high. In addition, short-term reproductive/developmental studies are not available for DEA. Section 4.1.2.2.1 provides information on effects on reproductive tissues after a 14-week exposure. In general, the amine class has not been shown to cause reproductive/developmental effects. A larger UF_D was not used because there were well-conducted subacute studies in both rats and mice, and a human study investigating sensory effects (which occurred at lower concentrations than respiratory tract effects).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 10 \text{ ppm} / (10 \text{ x } 3 \text{ x } 3)$$
$$= 10 \text{ ppm} / 90$$
$$= 0.1111 \text{ ppm}$$
$$= 110 \text{ ppb (rounded to two-significant figures)}$$

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

The acute ReV was rounded to two significant figures. The resulting 1-h acute ReV is 110 ppb (330 µg/m^3). The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 33 ppb (99 µg/m^3) (Table 7).

Table 8 provides a summary of the confidence in the different steps of the acute toxicity assessment based on guidance in Beck et al. (2015). The Lundqvist et al. (1992) study is considered a medium quality study and the confidence in the acute database is medium. The overall confidence in the toxicity assessment is medium.

Table 7 Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Summary**
Study	Lundqvist et al. (1992) 1-h subjective responses of 5 adults (Lundquist et al., 1992)
Study population	5 male adults (60-min)
Exposure methods	Climate Chamber (0-12 ppm for 60 min, average of 10 ppm)
Critical effects	Low to moderate nasal and eye irritation
POD	10 ppm (minimal LOAEL)
Exposure duration	1 h
Extrapolation to 1 h	N/A
POD_{ADJ} (1 h)	N/A
POD_{HEC}	10 ppm
Total uncertainty factors (UFs)	90
Interspecies UF	N/A
Intraspecies UF	10
LOAEL UF	3
Incomplete Database UF	3
acute ReV [1 h] (HQ = 1)	**330 µg/m^3 (110 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**99 µg/m^3 (33 ppb)**

Table 8 Confidence in the Acute Toxicity Assessment

Not Evaluated	Low Confidence	Medium Confidence	High Confidence
Validation Toxicity Value Comparison	Systematic Review Peer Review	Database Completeness Key Study Quality Point of Departure (POD) Sensitive Populations	Critical Effect Relevance of Critical Effect Human Equivalent POD (POD_{HEC})

Element	Score * (1-5)	Basis
Database Completeness	3 Medium	Short-term reproductive/developmental studies are lacking. MOA information is adequate
Systematic Review	1 Low	At the time of this assessment, TCEQ did not employ a systematic procedure for data gathering, analysis and internal review
Key Study Quality	3 Medium	Lundqvist et al. (1992) only made use of 5 subjects. In addition, the study design was not blind, although this might bias the study results high
Critical effect	5 High	Studies are sufficient to determine the critical effect with confidence based on MOA
Relevance of Critical Effect	5 High	The critical effect of low to moderate nasal and eye irritation was observed in humans and is consistent based on knowledge of MOA.
Point of Departure(POD)	2 medium	Only a minimal LOAEL (0-12 ppm for 60 min, average of 10 ppm) was identified for low to moderate nasal and eye irritation.
Human Equivalent POD (POD_{HEC})	5 High	Human data was available for a exposure duration of one hour. No duration or animal-to-human adjustment was needed
Sensitive Populations	2 Medium	There was no data to evaluate sensitive subpopulations or increased childhood susceptibility. TD assumed the UF_H of 10 was adequate
Peer Review	+ Low	The DSD will be posted for public comment
Validation	+ Low	No biological indices are available for comparison. Ambient air monitoring data from one study indicates measured ambient air DEA concentrations are well below the acute ReV
Toxicity Value Comparison	-	No other agencies have derived DEA acute inhalation toxicity values

* Criteria for scoring the individual elements are provided in Beck et al. (2015). For the first eight elements: Low (1), medium (2-3), high (4-5). For peer review, validation, and toxicity value comparison: low (+), medium (++), high (+++), or not evaluated (-).

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

DEA has a characteristic fishy, ammonia-like odor (NIOSH 2011). Nielsen and Yamagiwa (1989) demonstrated sensory irritation effects are an important part of odor sensation. The $^{acute}ESL_{odor}$ for DEA, based on an evidence-integration approach and historical information (TCEQ 2015). is 180 µg/m^3 (60 ppb) (50% recognition level from Hellman and Small 1974).

3.2.2 Vegetation Effects

No data were found regarding adverse short-term vegetation effects; therefore, an acute vegetation-based ESL was not developed.

3.3. Short-Term ESL

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

- acute ReV = 330 µg/m^3 (110 ppb)
- $^{acute}ESL$ = 99 µg/m^3 (33 ppb)
- $^{acute}ESL_{odor}$ = 180 µg/m^3 (60 ppb)

The short-term ESL for air permit evaluations is the $^{acute}ESL$ of 99 µg/m^3 (33 ppb) (Table 2).

3.4. Acute Inhalation Observed Adverse Effect Level

The LOAEL value of 10 ppm determined in humans from Lundqvist et al. (1992) (Table 7) is the acute 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. No duration adjustment was made (TCEQ 2012).

The $LOAEL_{HEC}$ determined from human studies represents a concentration where similar adverse effects may occur in humans exposed to the same level of concentration over the same duration as used in the study, or longer. However, effects are not a certainty due to potential intraspecies differences in sensitivity. The acute inhalation observed adverse effect level is provided for informational purposes only.

Chapter 4 Chronic Evaluation

NTP (2011) and Montelius (2013) recently reviewed the toxicity of DEA. The TCEQ reviewed the toxicity information in these documents and also conducted a thorough review of the literature since 2008.

4.1 Noncarcinogenic Potential

There are no published epidemiology studies or reports of chronic health effects in humans with adequate DEA exposure data, except as discussed in Section 3.1.2. Therefore, animal studies were used to derive the chronic ReV. After chronic exposure, DEA causes adverse effects in the respiratory tract at low concentrations, primarily in the upper respiratory tract. Systemic effects were not noted except at high concentrations (similar to acute effects).

4.1.1 Physical/Chemical Properties

The log K_{ow} of 0.58 for DEA is low, which indicates it is unlikely to bioconcentrate. The pKa is 11.09 (HSDB 2015). For other physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.2 Key and Supporting Studies (NTP 2011)

High-quality subchronic and chronic animal studies were conducted by NTP (2011), which produced the lowest NOAEL and LOAEL values when compared to two other subchronic animal studies. The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). The following sections focus on the 105-wk and 14-wk NTP (2011) studies. Table 12 provides a summary of pertinent subchronic inhalation studies. Appendix A (reproduced from NTP 2011) provides additional information on these subchronic inhalation studies.

4.1.2.1 Two-Year Key Animal Study - NTP (2011)

4.1.2.1.1 Study Details (NTP 2011)

F344/N rats and B6C3F1 mice were treated with DEA 6 h/d, 5 d/wk for 14 weeks and 105 wks. Both rats and mice were observed twice daily and were weighed initially and then weekly for the first 13 wks; clinical findings were recorded every 4 wks for the first 13 wks; afterwards, body weights and clinical findings were recorded every 4 wks through week 93; then every 2 wks, and at the end of the studies. Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eyes, gallbladder (mice only), Harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lungs, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, uterus, and Zymbal's gland (rats only). Full hematology and clinical chemistry parameters were evaluated in the 3-month study (discussed in Section 4.1.2.2), but not for the 2-year study.

4.1.2.1.2 Two-Year Study in Rats (NTP 2011)

Groups of 50 male and 50 female rats were exposed to DEA vapor at concentrations of 0, 31, 62.5, or 125 ppm, 6 h/d, 5 d/wk for 105 wks. Survival of exposed groups of rats was similar to that of the chamber control groups. Mean body weights of males and females exposed to 125 ppm were less than those of the chamber controls after week 57. Increased incidences of eye abnormality occurred in exposed males and females.

A spectrum of nonneoplastic lesions was observed in the respiratory and olfactory EPI of the nose in exposed rats. The lesions included suppurative inflammation, ulceration of the respiratory EPI, hyaline droplet accumulation in the glands of the respiratory EPI, necrosis of the turbinates, squamous metaplasia of the respiratory EPI, hyperplasia of the respiratory EPI, atrophy of the olfactory EPI, hyaline droplet accumulation in the respiratory and olfactory EPI, basal cell hyperplasia of the olfactory EPI, respiratory metaplasia of the olfactory EPI, and goblet cell hyperplasia.

The incidence of chronic inflammation of the pleura was significantly increased in 125 ppm females. The incidences of histiocytic cellular infiltration of the alveolus of the lung were significantly increased in all exposed groups of females and the incidence of chronic inflammation was significantly increased in 125 ppm females.

In 125 ppm males, the incidence of suppurative inflammation of the cornea was significantly increased.

4.1.2.1.3 Critical Effects from Two-Year Study in Rats

There were significant differences in accumulation of hyaline droplets in the respiratory EPI glands, olfactory EPI, and respiratory EPI. These effects were graded as minimal to mild (Table 17, Appendix C). Minimal to mild changes for accumulation of hyaline droplets are not considered adverse (NTP 2015). Hyaline droplet formation is a common occurrence in aged rodents (Ong et al. 2015).

Statistical differences in olfactory EPI, respiratory metaplasia; respiratory EPI, ulcer; Goblet cell, hyperplasia, and turbinate, necrosis only occurred at the highest concentration of 125 ppm and were not considered as the lowest, critical effects. Table 9 shows the incidences of nonneoplastic lesions of the nose in rats with the lowest LOAEL and NOAEL values that were significantly different from controls and had adequate concentration/response relationships. The LOAEL of 31 ppm from the rat study is based on atrophy in the olfactory EPI and hyperplasia of the respiratory EPI, effects statistically different from controls at 31 ppm (Table 9). A NOAEL from the rat study was not identified.

Table 9 Incidences of Lesions of the Nose in Rats in 2-Year Inhalation Study

Nonneoplastic Lesion	Sex	0 ppm (49 M, 50 F)	31 ppm (50 M, 49 F)	62.5 ppm (50 M, 50 F)	125 ppm (50 M, 50 F)
Inflammation, suppurative	M	5 [a] (1.6) [b]	5 (1.6)	10 (1.7)	29 ** (2.6)
Inflammation, suppurative	F	6 (2.0)	4 (1.5)	15 * (1.5)	34 ** (2.9)
Inflammation, suppurative	Sum	11	9	25	63
Olfactory EPI, atrophy	M	2 [a] (1.5) [b]	49 ** (1.5)	50 ** (1.8)	50 ** (2.3)
Olfactory EPI, atrophy	F	1 (1.0)	47 ** (1.9)	48 ** (2.3)	50 ** (2.7)
Olfactory EPI, atrophy	Sum	3	96	98	100
Respiratory EPI, hyperplasia	M	5 (1.6)	34 ** (1.2)	35 ** (1.3)	47 ** (1.9)
Respiratory EPI, hyperplasia	F	7 (1.4)	31 ** (1.2)	41 ** (1.4)	50 ** (2.4)
Respiratory EPI, hyperplasia	Sum	12	65	76	97
Respiratory EPI, Metaplasia, squamous	M	0	2 (1.0)	6 * (1.8)	26 ** (2.1)
Respiratory EPI, Metaplasia, squamous	F	1 (1.0)	1 (1.0)	5 (1.4)	39 ** (2.3)
Respiratory EPI, Metaplasia, squamous	Sum	1	3	11	65

[a] Number of animals with lesions.

[b] Average severity grade of lesions in affected animals (in parentheses): 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test.

** $P \leq 0.01$.

4.1.2.1.4 Two-Year Study in Mice (NTP 2011)

Groups of 50 male and 50 female mice were exposed to DEA vapor at concentrations of 0, 16, 31, or 62.5 ppm, 6 h/d, 5 d/wk for 105 wk. Survival of exposed groups of mice was similar to that of the chamber control groups. Mean body weights of males and females were similar to those of the chamber controls. Eye abnormality was observed in greater incidence in exposed groups of males than in the chamber controls, and torso/ventral ulcer/abscess was observed in six 62.5 ppm exposed males compared to none in the chamber controls.

A similar spectrum of nonneoplastic lesions was seen in the nose of exposed mice as was seen in rats, although mice were the most sensitive species. The concentrations that mice were exposed to were lower than the concentrations rats were exposed.

4.1.2.1.5 Critical Effects from Two-Year Study in Mice

There were significant differences in accumulation of hyaline droplets in the respiratory EPI glands and respiratory EPI. These effects were graded as minimal to mild (Table 18, Appendix C). Minimal to mild changes for accumulation of hyaline droplets are not considered adverse (NTP 2015). Hyaline droplet formation is a common occurrence in aged rodents (Ong et al. 2015).

Adverse effects that were statistically different from controls at the highest concentration of 62.5 ppm are as follows: glands, respiratory EPI, hyperplasia; chronic active inflammation of the glands of the respiratory EPI; suppurative inflammation; and necrosis of the respiratory EPI. These effects were not considered as the lowest, critical effects.

Table 10 shows the incidences of nonneoplastic lesions of the nose in mice with the lowest LOAEL and NOAEL values that were significantly different from controls and had adequate concentration/response relationships and increases in severity grades.

The effects that occurred at the lowest concentration (LOAEL of 16 ppm) from the mouse study are (1) atrophy in the olfactory EPI, (2) respiratory metaplasia in the olfactory EPI, and (3) hyperostosis in the turbinates (increase in the amount of bone resulting in a thickened anatomic structure). These effects had the best concentration response in both number of animals affected and increasing severity of lesions (minimal to moderate).

Table 10 Incidences of Lesions of the Nose in Mice in 2-Year Inhalation Study

Nonneoplastic Lesion	Sex	0 ppm (50 M, 50 F)	16 ppm (50 M, 49 F)	31 ppm (50 M, 50 F)	62.5 ppm (50 M, 50 F)
Olfactory EPI, atrophy	M	9 [a] (1.0) [b]	19 * (1.3)	50 ** (2.0)	50 ** (2.5)
Olfactory EPI, atrophy	F	8 (1.0)	29 ** (1.4)	49 ** (2.1)	50 ** (2.6)
Olfactory EPI, atrophy	Sum	17	48	99	100
Olfactory EPI, respiratory metaplasia	M	14 (1.0)	15 (1.7)	44 ** (2.3)	50 ** (3.0)
Olfactory EPI, respiratory metaplasia	F	4 (1.0)	15 ** (1.6)	48 ** (2.8)	50 ** (3.0)
Olfactory EPI, respiratory metaplasia	Sum	28	30	92	100
Respiratory EPI, metaplasia, squamous	M	4 (1.0)	7 (1.0)	16 ** (1.0)	34 ** (1.4)
Respiratory EPI, metaplasia, squamous	F	0	0	13 ** (1.1)	35 ** (1.3)
Respiratory EPI, metaplasia, squamous	Sum	4	7	29	69
Turbinate, Hyperostosis	M	5 (1.2)	23 ** (1.1)	50 ** (2.0)	50** (3.5)
Turbinate, Hyperostosis	F	4 (1.0)	23 ** (1.1)	49 ** (1.8)	50 ** (2.9)
Turbinate, Hyperostosis	Sum	9	46	99	100

[a] Number of animals with lesions.

[b] Average severity grade of lesions in affected animals (in parentheses): 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test.

** $P \leq 0.01$.

4.1.2.2 Supporting Animal Studies

4.1.2.2.1 Evaluation of Reproductive Tissues after 14 Wks (NTP 2011)

Groups of 10 male and 10 female rats/mice were exposed to DEA vapor at concentrations of 0, 8, 16, 32, 62, or 125 ppm, 6 h/d, 5 d/wk for 14 wks. There was no evidence of systemic toxicity associated with DEA exposure for 14 wks except for mice. The mean body weights of 125 ppm male and female mice were significantly less than those of the chamber controls. There were no exposure-related changes in hematology, serum chemistry indices, or organ weights of exposed rats or mice.

NTP (2011) evaluated reproductive tissues and estrous cycle characterization in both rats and mice after the 14-wk exposure. At the end of the studies, sperm samples were collected from male animals in the 0, 32, 62, and 125 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 days prior to the end of the studies from females exposed to 0, 32, 62, or 125 ppm for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.

In rats, all reproductive tissues and estrous cycle characterization parameters were not significantly different from controls except for the following:

- There were significant exposure concentration-related decreases in percent sperm motility in males at 32 ppm (4.7 % lower than controls), 62 ppm (6.2% lower than controls), and 125 ppm (26% lower than controls) (Table 11).

- There were no significant differences in the lengths of estrous cycles between chamber control and exposed groups of females.

- Exposure-related nasal lesions were seen primarily in rats exposed to 62 or 125 ppm. These lesions included turbinate necrosis, suppurative inflammation, respiratory epithelial hyperplasia, squamous metaplasia of the respiratory EPI, and olfactory epithelial atrophy.

In mice, reproductive tissues and estrous cycle characterization parameters were not significantly different from controls, except for the following:

- The mean body weights of 125 ppm males and females were significantly less than those of the chamber controls.

- There were significant exposure concentration-related decreases in sperm motility in males exposed to 32 ppm (7.0% lower than controls), 62 ppm (9.4% lower than controls), or 125 ppm (15% lower than controls) (Table 11).

- The estrous cycle of 125 ppm females was significantly longer than that of the chamber controls, but only by half a day.

- Histopathologic changes were noted primarily in the nasal cavity and involved both the respiratory and olfactory EPI of males and females principally in the 62 or 125 ppm groups. These lesions included suppurative inflammation, squamous metaplasia of the respiratory EPI, olfactory epithelial atrophy, and necrosis of the turbinates.

Table 11 Concentration-Dependent Decrease in Percent Sperm Motility (NTP 2011)

Concentration (number of animals)	Control (10)	32 ppm (10)	62 ppm (10)	125 ppm (10)
Rat Sperm motility (%)	93.01 ± 0.72	88.60 ± 1.45 ** (4.7% decrease)	87.27 ± 1.57 ** (6.2% decrease)	68.44 ± 2.78 ** (26% decrease)
Mouse Sperm motility (%)	86.66 ± 1.45	80.60 ± 1.41 ** (7.0% decrease)	78.47 ± 1.51 ** (9.4% decrease)	73.65 ± 2.04 ** (15.0% decrease)

* Means ± standard error (SE).

** Significantly different ($P < 0.01$) from the chamber control group by by Shirley's test (1977) (as modified by Williams (1986) and Dunn (1964)). Shirley's test is a nonparametric multiple comparison method used to evaluate typically skewed distributions.

4.1.2.2.2 Lynch et al. (1986)

Taken directly from NTP (2011)

> Early interest in the pharmacology of the simple aliphatic amines was initially stimulated by their structural relationship with epinephrine. The aliphatic amine hydrochlorides were observed to have sympathomimetic activity (increased blood pressure) when given intravenously (Barger and Dale, 1911). Repeated administration of the amines resulted in cardiac depression and vasodilatation (Ahlquist, 1945). Brieger and Hodes (1951) reported that triethylamine caused significant cardiac muscle degeneration in rabbits. Diethylamine was reported to cause a slight, questionable increase in cardiac degeneration in rabbits. Lynch et al. (1986) exposed male and female Fischer 344 rats to 25 or 250 ppm

diethylamine 6.5 h/d, 5 d/wk, for up to 6 months to more fully investigate the potential cardiac toxicity reported by Brieger and Hodes (1951). Rats exposed to 250 ppm had decreased body weights and nasal cavity lesions including squamous metaplasia, rhinitis, and lymphoid hyperplasia. There were no treatment-related effects in rats exposed to 25 ppm diethylamine. Measurements of cardiotoxicity were all negative in exposed rats. Electrocardiograms (ECGs) were recorded from 10 rats per sex per group just prior to terminal sacrifice. There were no changes in ECGs or cardiac-related clinical chemistry indices. There was no histological evidence of cardiac muscle degeneration.

4.1.2.3 Summary of Chronic and Subchronic Inhalation Studies

The NTP (2011) was a higher quality study when compared to other subchronic studies. Table 12 provides a summary of pertinent subchronic and the one chronic inhalation study (arranged from lowest to highest concentrations). Appendix A (reproduced from NTP 2011) provides additional information on subchronic inhalation studies.

Table 12 Chronic and Subchronic Inhalation Studies

Exposure Concentration (species)	Exposure (Number/sex/dose)	NOAEL	LOAEL	Notes (References)
0, 16, 31, or 62.5 ppm (B6C3F1 Mice) [a]	105 wk, 6 h/d, 5 d/wk (50 M, 50 F)	- - -	16 ppm [a]	A spectrum of nonneoplastic lesions was observed in the respiratory and olfactory EPI of the nose (NTP 2011)
0, 31, 62.5, or 125 ppm (F344/N Rats)	105 wk, 6 h/d, 5 d/wk (50 M, 50 F)	- - -	31 ppm	A spectrum of nonneoplastic lesions was observed in the respiratory and olfactory EPI of the nose (NTP 2011)
0, 32, 62, or 125 ppm (B6C3F1 Mice) [a]	14 wk, 6 h/d, 5 d/wk (10 M, 10 F)	- - -	32 ppm	Statistical decrease in sperm motility (NTP 2011)
0, 32, 62, or 125 ppm (F344/N Rats)	14 wk, 6 h/d, 5 d/wk (10 M, 10 F)	- - -	32 ppm	Statistical decrease in sperm motility (NTP 2011)
50 ppm (Rabbits)	6 wk, 7 h/d, 5 d/wk	- - -	50 ppm	Severe ocular irritation (Brieger and Hodes 1951 (referenced in NTP 2011))
25 or 250 ppm (Fisher 344 rats)	24 wk, 6.5 h/d, 5 d/wk (M, F)	25 ppm[b]	250 ppm	Severe ocular irritation. At 250 ppm, decreased body weights and nasal cavity lesions including squamous metaplasia, rhinitis, and lymphoid hyperplasia. Nasal histopathology was not performed at 25 ppm. Measurements of cardiotoxicity were all negative in exposed rats (Lynch et al. 1986)

[a] Study with lowest LOAEL level.

[b] Nasal histopathology was not performed at 25 ppm.

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

4.1.3.1 MOA

DEA is corrosive and strongly alkaline, with a pKa of 11.09 (HSDB 2015). When amines with a high pKa come in contact with tissues or fluids at physiologic pH, they become protonated and hydroxide ion is released, causing local necrosis (See Figure 1). It is irritating to the skin and mucous membranes (NTP 2011). DEA is assumed to have a threshold MOA and is relevant to humans.

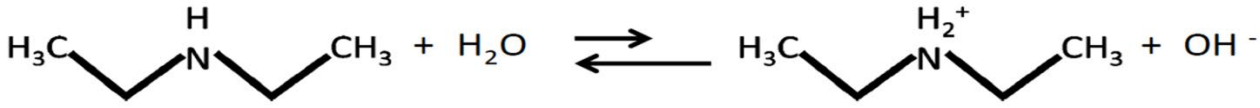


Figure 1 Chemical Reaction Showing the Protonation of DEA and Creation of a Hydroxide Ion.

The mechanisms for hyperostosis observed in mice were discussed by NTP (2011). The proposed mechanism is based on DEA's strongly alkaline properties (taken directly from NTP 2011):

> Mechanisms of hyperostosis may be divided into proliferative and nonproliferative categories, based upon evidence of either increased bone cell proliferation or decreased bone resorption, respectively (Long *et al.*, 1993). Since the nasal turbinate bone of diethylamine exposed mice in the 2-year study was histologically quiescent (without osteoblastic or osteoclastic activity), the pathogenesis of the bone thickening was uncertain. However, both proliferative and nonproliferative mechanisms could be involved. In the 3-month mouse study, slight thickening of nasal turbinates was noted and this was accompanied by activation of mesenchymal osteoprogenitor cells, indicative of a proliferative response (Rosenberg, 2009). In addition, an imbalance of normal bone remodeling activity associated with decreased bone resorption could have resulted from neutralization of the normally acidic osteoclast resorption pit by the marked alkalinity of diethylamine.

4.1.3.2 Dose Metric

The exposure concentration of the parent chemical was used as the dose metric.

4.1.4 Benchmark Dose Modeling

4.1.4.1 Respiratory Effects

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.4) for the data in Tables 9 and 10, which were taken from the NTP (2011) rat and mouse study. Data were used to predict 95% lower confidence limits on the BMCs ($BMCL_{10}$) and the central estimate (BMC_{10}) using dichotomous models. A default benchmark response (BMR) of 10% was selected for extra risk for the BMC_{10} and $BMCL_{10}$.

BMC modeling was conducted on the combined male and female data for each of the histological endpoints that showed a dose response relationship and had at least two recorded incidences past the control value, making them suitable for BMC modeling. All of the available dichotomous models were run and the results can be found in Appendix E. The best fit models for each of the histological end points are listed in Table 13 along with their detailed results. Data for atrophy of rat olfactory EPI were not amenable to BMC modeling (the dose-response was too steep), so the LOAEL of 31 ppm was used at the POD for that endpoint (Table 13).

Table 13 BMC Results for the Best Fit Model for the Examined Endpoints

Endpoint	Best Model	p value	AIC	Scaled Residual	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Rat inflammation, suppurative	Dichotomous-Hill	0.637	379.87	< | 2 |	60.3	48.8
Rat atrophy of olfactory EPI	No acceptable models	---	---	---	LOAEL 31 ppm	---
Rat respiratory EPI, hyperplasia	Gamma Multistage 2	0.150	345.37	< | 2 |	4.23	3.66
Rat respiratory EPI Metaplasia squamous	Logistic	0.981	240.90	< | 2 |	61.5	54.1
Mouse atrophy in the olfactory EPI	Multistage 3^0	0.746	244.16	< | 2 |	9.30	6.08
Mouse respiratory metaplasia in the olfactory EPI	Gamma	0.935	299.94	< | 2 |	17.1	14.3
Mouse respiratory EPI metaplasia squamous	Multistage 2°	0.480	333.99	< | 2 |	19.0	15.3
Mouse hyperostosis in the turbinates [a]	**Multistage 3^0**	**0.866**	**212.76**	**< | 2 |**	**9.13**	**5.71**

[a] chosen as the critical effect.

4.1.4.2 Reproductive Effects Compared to Respiratory Effects

NTP (2011) noted a statistical significant decrease in the percent sperm motility in both rats and mice following exposure to 32 ppm DEA for 14 wks. Decrease in sperm motility data from Table 11 was modeled using continuous models for both rats and mice. A default BMR of 1 standard deviation (SD) was used (the standard BMR for continuous data (TCEQ 2012)) and the 95% lower confidence limits on the $BMC_{1\ SD}$ were calculated. However, these data were not

amenable to BMC modeling. Therefore, the POD for reproductive effects is the LOAEL of 32 ppm.

The LOAELs based on respiratory effects are lower than the LOAEL of 32 ppm for decrease in sperm motility (Table 12). The BMC_{10} of 9.13 ppm and $BMCL_{10}$ of 5.71 ppm for hyperostosis in the turbinates observed in mice are lower than the LOAEL of 32 ppm for decrease in sperm motility. Therefore, if effects in the respiratory tract are prevented, then reproductive effects in male mice and rats will be prevented.

4.1.5 Critical Effect and POD

4.1.5.1 Respiratory Effects

Table 13 provides results for BMC modeling for the adverse effects noted in the NTP (2011) study. Hyperplasia of respiratory EPI in the rat had the lowest $BMCL_{10}$ value of 3.66 ppm whereas the next highest $BMCL_{10}$ value of 5.71 ppm was obtained for hyperostosis in the turbinates in mouse. However, hyperostosis in the turbinates in mouse had the best concentration response in both number of animals affected and increasing severity of lesions (mild to moderate) with the lowest LOAEL of 16 ppm (Table 14). The average severity of lesions for hyperplasia of respiratory EPI in rats at 31 ppm, the LOAEL value, were lower than or equal to the control value and were of minimal severity (Table 14). Therefore, hyperplasia of respiratory EPI in rats was not considered as the critical effect. The critical effect is hyperostosis in the turbinates in mouse.

Table 14 Comparison of Critical Effects Observed in the Rat and Mouse Studies

Nonneoplastic Lesion	Sex	0 ppm	16 ppm	31 ppm	62.5 ppm	125 ppm
Rat Respiratory EPI, hyperplasia	M	5 [a] (1.6 [b])	- - -	34 ** (1.2)	35 ** (1.3)	47 ** (1.9)
Rat Respiratory EPI, hyperplasia	F	7 (1.4)	- - -	31 ** (1.2)	41 ** (1.4)	50 ** (2.4)
Rat Respiratory EPI, hyperplasia	Sum	12	- - -	65	76	97
Mouse Turbinate, Hyperostosis	M	5 (1.2)	23 ** (1.1)	50 ** (2.0)	50** (3.5)	- - -
Mouse Turbinate, Hyperostosis	F	4 (1.0)	23 ** (1.1)	49 ** (1.8)	50 ** (2.9)	- - -
Mouse Turbinate, Hyperostosis	Sum	9	46	99	100	- - -

[a] Number of animals with lesions.

[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test.

** $P \leq 0.01$.

NTP (2011) regarded the mouse as the most sensitive species and the TCEQ agrees with this observation. Therefore, the critical effect is hyperostosis in the turbinates observed in the mouse with a $BMCL_{10}$ value of 5.71 ppm. Since duration adjustments and dosimetric adjustments are identical for the rat and mouse POD, identifying the critical effect of hyperostosis in the turbinates observed in mice is defensible at this stage of the assessment. As mentioned previously, if effects in the respiratory tract are prevented, then reproductive effects in male mice and rats will be prevented.

4.1.6 Dosimetric Adjustments

4.1.5.1 Default Exposure Duration Adjustments

The effects of DEA are assumed to be concentration and duration dependent. An adjustment from a discontinuous to a continuous exposure duration was conducted (TCEQ 2012) as follows:

POD_{ADJ} = POD x (D/24 h) x (F/7 d)

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

POD_{ADJ} = 5.71 ppm x (6/24) x (5/7) = 1.020 ppm

4.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

The health effects produced by DEA at lower concentrations are respiratory tract effects in the extrathoracic (ET) region of the respiratory tract, so dosimetric adjustments were performed as a Category 1 vapor based on updated recommendations in USEPA (2012) in order to calculate a POD_{HEC}. A default value of 1 was used for the Regional Gas Dose Ratio (RGDR) for a Category 1 gas with ET respiratory effects (USEPA 2012).

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

$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$

= 1.020 ppm x 1

= 1.020 ppm or 1,020 ppb

4.1.7 Adjustment of POD_{HEC} and Application of Uncertainty Factors

The lowest POD_{HEC} of 1,020 ppb from the NTP (2011) chronic study was based on hyperostosis in the turbinates in the mouse study by NTP (2011). The default for noncarcinogenic effects is to determine a POD_{HEC} and apply UFs to extrapolate from the POD to lower concentrations (i.e., assume a threshold MOA) in order to calculate a ReV. To calculate the chronic ReV, the POD_{HEC} was divided by appropriate UFs, for a total UF of 90:

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

- A UF_A of 3 was used because a default dosimetric adjustment from animal-to-human exposure was conducted, which accounts for toxicokinetic differences but not toxicodynamic differences.
- A UF_L of 1 was used because BMC modeling was conducted and the resulting POD ($BMCL_{10}$) is considered a NOAEL.
- UF_D of 3 was used because there is one chronic study conducted in rats and mice (NTP 2011) and a chronic study in rats (Lynch et al. 1986). There was a 14-week reproductive study conducted in rats and mice (NTP 2011) that indicated a decrease in sperm motility, at higher concentrations than upper respiratory effects. A higher UF_D was not used because MOA information was available and deemed to be relevant for humans. Short-term developmental or reproductive toxicity data in experimental animals or humans were not found in the literature. In general, the amine chemical class has not been shown to cause reproductive/developmental effects.

Chronic ReV= POD_{HEC} / (UF_H x UF_A x UF_L x UF_D)
= 1,020 ppb / (10 x 3 x 1 x 3)
= 1,020 ppb / 90
= 11.33 ppb

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

The chronic ReV value was rounded to two significant figures. The resulting chronic ReV is 11 ppb (33 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target HQ of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 3.3 ppb (9.9 µg/m^3) (Table 15).

Table 16 provides a summary of the confidence in the different steps of the chronic toxicity assessment based on guidance in Beck et al. (2015). Database completeness was medium and study quality was high. The overall confidence in the toxicity assessment was medium to high.

Table 15 Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	**Summary**
Study	105 week bioassay (NTP 2011)
Study Population	F344/N rats and B6C3F1 mice, 50 males and 50 females/group
Exposure Method	Exposures via inhalation to analytical concentrations of DEA vapor Rats: 0, 31, 62.5, or 125 ppm, Mice: 0, 16, 31, or 62.5 ppm
Critical Effects	Hyperostosis in the turbinates in mouse
POD for observed adverse effect level (BMC_{10})	9.13 ppm
POD ($BMCL_{10}$)	5.71 ppm
Exposure Duration	6 h/d, 5 d/wk for 105 wks
Extrapolation to continuous exposure (POD_{ADJ})	1.020 ppm or 1,020 ppb
POD_{HEC}	1,020 ppb
Total UFs	90
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	1
Incomplete database UF	3
Chronic ReV (HQ = 1)	**33 µg/m^3 (11 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**9.9 µg/m^3 (3.3 ppb)**

Table 16 Confidence in the Chronic Toxicity Assessment

Not Evaluated	Low Confidence	Medium Confidence	High Confidence
Validation Toxicity Value Comparison	Systematic Review Peer Review	Database Completeness Human Equivalent POD Sensitive Populations	Key Study Quality Critical Effect Relevance of Critical Effect Point of Departure

Element	Score * (1-5)	Basis
Database Completeness	3 Medium	One chronic study in rats and mice, and one chronic study in rats. Short-term reproductive/developmental studies are lacking. MOA information is adequate
Systematic Review	1 Low	At the time of this assessment, TCEQ did not employ a systematic procedure for data gathering, analysis and internal review
Key Study Quality	5 High	The chosen study is well done
Critical effect	5 High	Studies are sufficient to determine the critical effect with confidence based on MOA
Relevance of Critical Effect	5 High	The critical effect of adverse upper respiratory effects is relevant to humans based on knowledge of MOA. Critical effect matches human experience
Point of Departure(POD)	5 High	A lower limit on the BMC was used as the POD. Multiple dose groups. Difference between BMC and BMCL was less than a factor of two.
Human Equivalent POD (POD_{HEC})	3 Medium	Default duration and dosimetric adjustments were made, which are assumed to be conservative
Sensitive Populations	2 Medium	There was no data to evaluate sensitive subpopulations or increased childhood susceptibility. TD assumed the UF_H of 10 was adequate
Peer Review	+ Low	The DSD will be posted for public comment
Validation	+ Low	No biological indices are available for comparison. Ambient air monitoring data from one study indicates measured ambient air DEA concentrations are well below the chronic ReV
Toxicity Value Comparison	-	No other agencies have derived DEA chronic inhalation toxicity values

* Criteria for scoring the individual elements are provided in Beck et al. (2015). For the first eight elements: Low (1), medium (2-3), high (4-5). For peer review, validation, and toxicity value comparison: low (+), medium (++), high (+++), or not evaluated (-).

4.2 Carcinogenic Potential

Based on the Guidelines for Carcinogen Risk Assessment (USEPA 2005a), the most appropriate cancer classification descriptor for DEA would be not likely to be carcinogenic to humans via the inhalation pathway. NTP (2011) concluded there was no evidence of carcinogenic activity for DEA. After review of the genetic toxicity data and 2-year study conducted by NTP (2011) the TCEQ agrees with NTP and concludes that there is no evidence of carcinogenic activity for DEA via the inhalation route.

4.2.1 Genetic Toxicology

The NTP (2011) reviewed previous genetic toxicity tests (reproduced in Appendix F). Published data provided no evidence of DEA-associated genotoxicity, although data from mammalian cell studies were limited.

The NTP (2011) genetic toxicity results are summarized as follows (taken directly from NTP 2011):

> Diethylamine was not mutagenic in either of two independent bacterial mutagenicity assays, each conducted with and without exogenous metabolic activation enzymes. Bacterial strains tested included Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and Escherichia colistrainWP2 uvrA/pKM101. In addition to the negative results the two bacterial assays, no significant increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male or female B6C3F1 mice from the 3-month study.

4.2.2 Carcinogenicity

The NTP (2011) reviewed the evidence that DEA was carcinogenic (reproduced in Appendix F). No epidemiology studies or case reports examining DEA exposure and cancer risk in humans were found in the literature. Limited oral studies indicate no carcinogenic potential (see Appendix F).

The NTP (2011) carcinogenicity conclusions are summarized as follows:

> Under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity of diethylamine in male or female F344/N rats exposed

to 31, 62.5, or 125 ppm. There was no evidence of carcinogenic activity of diethylamine in male or female B6C3F1 mice exposed to 16, 31, or 62.5 ppm.

Exposure to diethylamine resulted in increased incidences of nonneoplastic lesions of the nose in male and female rats and mice, of the cornea in male rats, and of the pleura and lung in female rats.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation effects; therefore, a welfare-based chronic ESL was not developed.

4.4 Long-Term ESL

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

- Chronic ReV = 33 µg/m^3 (11 ppb)
- $^{chronic}ESL_{threshold(nc)}$= 9.9 µg/m^3 (3.3 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 9.9 µg/m^3 (3.3 ppb) (Table 2).

4.5 Chronic Observed Adverse Effect Level

The critical endpoint used in the chronic evaluation, hyperostosis in the turbinates in mouse (the most sensitive species), was also used as the basis for calculation of a chronic inhalation observed adverse effect level. The BMC_{10} value of 9.13 ppm determined using data from the NTP study (2011) was used as a LOAEL (Table 15). 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. No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to calculate a $LOAEL_{HEC}$ of 9.13 ppm (use of an RGDR of 1).

The $LOAEL_{HEC}$ determined from an animal study, where effects occurred in some animals, represents a concentration at which similar effects may 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 chronic inhalation observed adverse effect level of 9.1 ppm (27 mg/m^3) (rounded to two significant figures) is provided for informational purposes only (TCEQ 2012).

The acute inhalation observed adverse effect level is based on the LOAEL value of 10 ppm determined in humans from Lundqvist et al. (1992) (Table 7), which was based on a moderate to strong olfactory response and distinct nasal and eye irritation. The acute and chronic observed

adverse effect levels are similar. This indicates that sensory irritation and adverse effects on the respiratory system after chronic exposure may occur at similar concentrations.

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Appendix A Review of DEA Toxicity Studies (NTP 2011)

Directly from NTP (2011):

> The acute toxicity of diethylamine has been investigated in various animal species by a variety of exposure methods. The LC_{50} in rats was reported as 4,000 ppm for a 4-hour inhalation exposure, and the oral LD50 ranges from 540 to 1,000 mg/kg in rats and 500 to 650 mg/kg in mice (Sax, 1996). Severe toxicity leading to death occurred in Sherman rats administered a single dose of 500, 1,000, or 2,000 mg/kg diethylamine by gavage (Union Carbide, 1950). In albino rats, mice, and guinea pigs administered diethylamine hydrochloride by gavage (dose not provided), toxicity was characterized by a decrease in motor activity and excitability (Saratikov et al., 1984). No gross lesions were observed at necropsy.
>
> The dermal LD_{50} ranges from 580 to 820 mg/kg in rabbits (Sax, 1996). Dermal contact with neat diethylamine for 24 hours caused mild irritation of rabbit skin (Union Carbide, 1950; Smyth et al., 1951). Instillation of 100 µL of 2% diethylamine into the eyes of rabbits caused redness, swelling, and corneal damage (Jacobs and Martens, 1989). Severe ocular irritation was also reported after inhalation exposure of rabbits to 50 ppm (150 mg/m^3) diethylamine for 7 hours per day, 5 days per week, for up to 6 wks (Brieger and Hodes, 1951) and in rats exposed to 250 ppm (750 mg/m^3) 6.5 hours per day, 5 days per week, for up to 6 months (Lynch et al., 1986).
>
> Acute inhalation exposure (60 to 600 ppm for 15 minutes) of male OF1 mice produced expiratory bradypnea indicative of upper airway irritation (Gagnaire et al., 1989). The calculated concentration resulting in a 50% decrease in respiratory rate (RD_{50}) was 202 ppm. Exposure of groups of six rats each to 1,000, 2,000, 4,000, or 8,000 ppm or saturated diethylamine for 4 hours resulted in the death of one rat at 2,000 ppm, three rats at 4,000 ppm, and all six rats in the 8,000 ppm and saturated vapor groups (Union Carbide, 1950). Irritation of the nose and eyes, tremors, and poor coordination were observed after 4 hours of exposure to 4,000 ppm. Exposure to 8,000 ppm caused convulsions, bloody discharge from the nose, and severe irritation of the ears and feet. Exposure to saturated vapor caused extreme congestion of the lungs, liver, kidneys, and spleen, as well as convulsions, loud rales, and corneal opacity (Union Carbide, 1950).
>
> In a subchronic inhalation study, male and female F344/N rats and B6C3F1 mice were exposed to 250 or 1,000 ppm diethylamine for 6 hours per day, 5 days per week, for up to 16 days (NIOSH, 1987). Acute ulcerative necrotizing

rhinitis and squamous metaplasia of the nasal mucosa were present in all exposed mice, with turbinate atrophy present in some animals. Squamous metaplasia of the tracheal mucosa was observed in the rats exposed to 1,000 ppm. Acute peribronchiolar pneumonia was also observed in the lungs of several rats exposed to 1,000 ppm and one rat exposed to 250 ppm. No treatment-related effects were observed in the heart, coronary arteries, or aorta. The nasal cavity was also the target site in male and female Fischer 344 rats exposed to 500 ppm diethylamine for 10 days (NIOSH, 1984). A moderate to marked necrotizing inflammation of the nasal mucosa was reported.

Early interest in the pharmacology of the simple aliphatic amines was initially stimulated by their structural relationship with epinephrine. The aliphatic amine hydrochlorides were observed to have sympathomimetic activity (increased blood pressure) when given intravenously (Barger and Dale, 1911). Repeated administration of the amines resulted in cardiac depression and vasodilatation (Ahlquist, 1945). Brieger and Hodes (1951) reported that triethylamine caused significant cardiac muscle degeneration in rabbits. Diethylamine was reported to cause a slight, questionable increase in cardiac degeneration in rabbits. Lynch et al. (1986) exposed male and female Fischer 344 rats to 25 or 250 ppm diethylamine 6.5 hours per day, 5 days per week, for up to 6 months to more fully investigate the potential cardiac toxicity reported by Brieger and Hodes (1951). Rats exposed to 250 ppm had decreased body weights and nasal cavity lesions including squamous metaplasia, rhinitis, and lymphoid hyperplasia. There were no treatment-related effects in rats exposed to 25 ppm diethylamine. Measurements of cardiotoxicity were all negative in exposed rats. Electrocardiograms (ECGs) were recorded from 10 rats per sex per group just prior to terminal sacrifice. There were no changes in ECGs or cardiac-related clinical chemistry indices. There was no histological evidence of cardiac muscle degeneration. In a comparable inhalation study of triethylamine (Lynch et al., 1990) male and female rats were exposed to 0, 25, or 247 ppm triethylamine vapor 6 hours per day, 5 days per week, for up to 28 wks. No physiologic or pathologic evidence of cardiotoxicity was seen in rats exposed to either concentration of triethylamine.

The potential immunotoxicity of diethylamine was investigated in a two-stage sensitization test using female CF1 (BR) albino mice (USEPA, 1987). A 0.1 mL dose of a 1.0% (v/v in 70% ethanol) diethylamine solution was applied to the abdomen of mice on days 0, 1, 2, and 3 of the study. The mice were challenged on day 10 by applying 0.01 mL of a 50% (v/v in 70% ethanol) diethylamine solution to the dorsal and ventral surfaces of the left ear. Animals were challenged again on day 17 using the dorsal and ventral surfaces of the

right ear. Mice were examined on study days 11, 12, 18, and 19 for changes in ear thickness of at least 20%, and no changes were detected.

Humans

Diethylamine is toxic if inhaled or swallowed or if it comes in contact with the eyes or skin. Severe eye damage has been reported after exposure to diethylamine vapor or contact with the liquid; in a case of accidental exposure of the eyes to liquid diethylamine, severe corneal damage with some permanent visual impairment was reported (OSHA, 1981). Long-term ocular exposure to diethylamine vapor may cause corneal edema resulting in temporary foggy vision and the appearance of halos around lights.

The acute effects of diethylamine vapor on the nasal cavity were evaluated in adult volunteers (Lundqvist et al., 1992). Exposure of five men to 25 ppm diethylamine for 15 minutes did not cause changes in nasal volume or nasal airway resistance. In a subsequent experiment, the acute sensory effects of diethylamine were evaluated in five men during exposure to increasing concentrations from 0 to 12 ppm for 1 hour. Subjective sensations including perceived odor intensity and sensory irritation, termed nose and eye irritation, were registered on a linear scale. A moderate to strong olfactory response and distinct nasal and eye irritation were reported.

APPENDIX B POD_{HEC} from the NTP (2011) Two-Week Study in Mice

POD and Critical Effect in Two-Week Study in Mice (NTP 2011)

The critical effect was based on minimal necrosis of the turbinates in 5 male mice and 4 female mice at 31 ppm DEA (LOAEL).

Dosimetric Adjustments

The POD of 31 ppm was adjusted from a 6-h exposure to a 1-h exposure concentration using Haber's rule as modified by ten Berge (1986) with a default value of "n"=3 (TCEQ 2012).

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(31 \text{ ppm})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 56.33 \text{ ppm} = POD_{ADJ}$$

The POD_{ADJ} of 56.33 ppm was then adjusted from an animal concentration to a human equivalent concentration (POD_{HEC}). DEA was considered a Category 1 vapor with effects observed in the ET region. Therefore, the POD_{ADJ} was adjusted from an animal concentration to a POD_{HEC} using a default value of one as RGDR for the ET region (TCEQ 2014b). The resulting minimal LOAEL POD_{HEC} is 56.33 ppm.

This value is 5-6 times higher than the POD_{HEC} from the human study of 10 ppm (i.e., the minimal LOAEL for sensory irritation).

Appendix C Nonadverse Responses in Rats and Mice (NTP 2011)

Table 17 Incidences of Nonadverse [a] Responses in Rats (NTP 2011) [a]

	Sex	0 ppm (49 M, 50 F)	31 ppm (50 M, 49 F)	62.5 ppm (50 M, 50 F)	125 ppm (50 M, 50 F)
Glands, respiratory EPI, accumulation, hyaline droplet	M	6 [b] (1.0) [b]	45 ** (1.2)	42 ** (1.6)	45 ** (1.5)
Glands, respiratory EPI, accumulation, hyaline droplet	F	9 (1.0)	46 ** (1.6)	45 ** (1.7)	44 ** (1.6)
Glands, respiratory EPI, accumulation, hyaline droplet	Sum	15	91	87	89
Olfactory EPI, accumulation, hyaline droplet	M	8 (1.0)	49 ** (2.4)	49 ** (2.1)	42 ** (1.7)
Olfactory EPI, accumulation, hyaline droplet	F	11 (1.3)	49 ** (2.6)	50 ** (2.6)	48 ** (2.4)
Olfactory EPI, accumulation, hyaline droplet	Sum	19	98	99	90
Respiratory EPI, accumulation, hyaline droplet	M	0	29 ** (1.2)	42 ** (1.4)	11 ** (1.5)
Respiratory EPI, accumulation, hyaline droplet	F	4 (1.0)	48 ** (1.9)	46 ** (1.2)	39 ** (1.4)
Respiratory EPI, accumulation, hyaline droplet	Sum	4	77	88	50

[a] NTP (2015).

[b] Number of animals with lesions.

[c] Average severity grade of lesions in affected animals (in parentheses): 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
** $P < 0.01$.

Table 18 Incidences of Nonadverse Responses [a] in Mice (NTP 2011)

	Sex	0 ppm (49 M, 50 F)	16 ppm (50 M, 49 F)	31 ppm (50 M, 50 F)	62.5 ppm (50 M, 50 F)
Glands, respiratory EPI, accumulation, hyaline droplet	M	5 [b] (1.0)[c]	5 (1.0)	16 ** (1.3)	33 ** (1.5)
Glands, respiratory EPI, accumulation, hyaline droplet	F	16 (1.3)	28 ** (1.4)	45 ** (1.9)	42 ** (1.8)
Glands, respiratory EPI, accumulation, hyaline droplet	Sum	21	33	61	75
Respiratory EPI, accumulation, hyaline droplet	M	11 (1.0)	6 (1.3)	19 (1.5)	30 ** (1.1)
Respiratory EPI, accumulation, hyaline droplet	F	20 (1.7)	33 ** (1.3)	47 ** (2.2)	29 (1.1)
Respiratory EPI, accumulation, hyaline droplet	Sum	31	39	66	59

[a] NTP (2015).

[b] Number of animals with lesions.

[c] Average severity grade of lesions in affected animals (in parentheses): 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

** $P < 0.01$.

Appendix D Benchmark Concentration Modeling for Rat Data

D.1 BMDS Summary of Rat Inflammation Suppurative

Table 19 Summary of BMD Modeling Results for Rat Inflammation Suppurative

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	0.342	380.57	53.2	40.2
Dichotomous-Hill	**0.637**	**379.87**	**60.3**	**48.8**
Logistic	0.104	382.06	38.8	34.2
LogLogistic	0.324	380.65	52.9	40.4
Probit	0.0551	383.28	35.8	31.6
LogProbit	0.449	380.23	53.4	41.5
Weibull	0.248	381.03	52.6	39.0
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.222	381.20	52.6	38.5
Multistage 2°	0.280	380.26	43.8	36.1
Quantal-Linear	1.00E-04	398.07	21.0	17.2

[a] Selected model in bold; scaled residuals for selected model for doses 0, 31, 62.5, and 125 were 0.33, -0.33, 0, 0, respectively. Basis for model selection is the lowest AIC
[b] BMD or BMDL computation failed for this model.

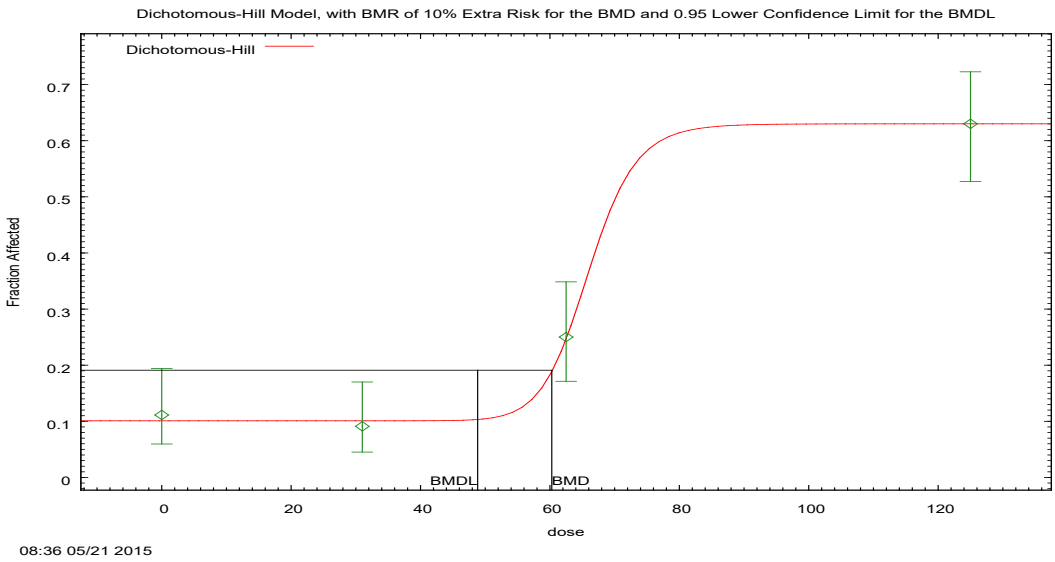

Figure 2 Incidence Rate by Dose for Rat Inflammation Suppurative

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Warning: BMDL computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 60.2842

BMDL at the 95% confidence level = 48.8302

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	0.630005	1
g	0.160332	0.111111
intercept	-7.5369E+01	-1.8913E+01
slope	18	4.041

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-186.82	4			
Fitted model	-186.93	3	0.222822	1	0.64
Reduced model	-232.67	1	91.6996	3	<.0001

AIC: = 379.868

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.101	10	11	99	0.33
31	0.101	10	9	99	-0.33
62.5	0.25	25	25	100	0
125	0.63	63	63	100	0

Chi^2 = 0.22 d.f = 1 P-value = 0.6372

D.2 BMDS Summary of Rat Olfactory EPI Atrophy

Table 20Summary of BMD Modeling Results for Rat Olfactory EPI Atrophy

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma[b] Weibull[c] Multistage 3°[d] Multistage 2° Quantal-Linear	0.0164	116.12	1.21	0.975
Dichotomous-Hill	0.312	114.15	0.937	0.0211
Logistic	0	124.08	4.61	3.55
LogLogistic	0.312	114.15	0.937	0.0509
Probit	0	136.68	4.51	3.71
LogProbit	0.330	114.03	0.269	6.96E-35
Multistage 4°	error	error	error[e]	error[e]

[a] No model was selected as a best-fitting model.
[b] For the Gamma and Weibull models, the power parameter estimates were 1 (boundary of parameter space).For the Gamma model, the power parameter estimate was 1. The model is equivalent to the Quantal-Linear model.
[c] For the Weibull and Gamma models, the power parameter estimates were 1 (boundary of parameter space).For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[e] BMD or BMDL computation failed for this model.

D.3 BMDS Summary of Rat Respiratory EPI, Hyperplasia

Table 21 Summary of BMD Modeling Results for Rat Respiratory EPI, Hyperplasia

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma[b] Multistage 2°[c]	**0.150**	**345.37**	**4.23**	**3.66**
Dichotomous-Hill[d]	0.0163	349.59	6.85	2.73
Logistic	3.00E-04	358.14	9.69	8.44
LogLogistic[e]	0.0163	349.59	6.85	2.73
Probit	1.00E-04	361.00	9.85	8.73
LogProbit	0.0271	348.59	6.97	2.84
Weibull[f] Quantal-Linear[g]	**0.150**	**345.37** [c]	**4.23**	**3.66**
Multistage 4°	error	error	error[h]	error[h]
Multistage 3°	0.0524	347.34	4.30	3.66

[a] Selected model in bold; scaled residuals for selected model for doses 0, 31, 62.5, and 125 were -0.16, 1.22, -1.44, 0.46, respectively. Basis for model selection is the Lowest AIC
[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[c] The Multistage 2° model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[d] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[e] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.
[f] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[g] The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Multistage 2° model.
[h] BMD or BMDL computation failed for this model.

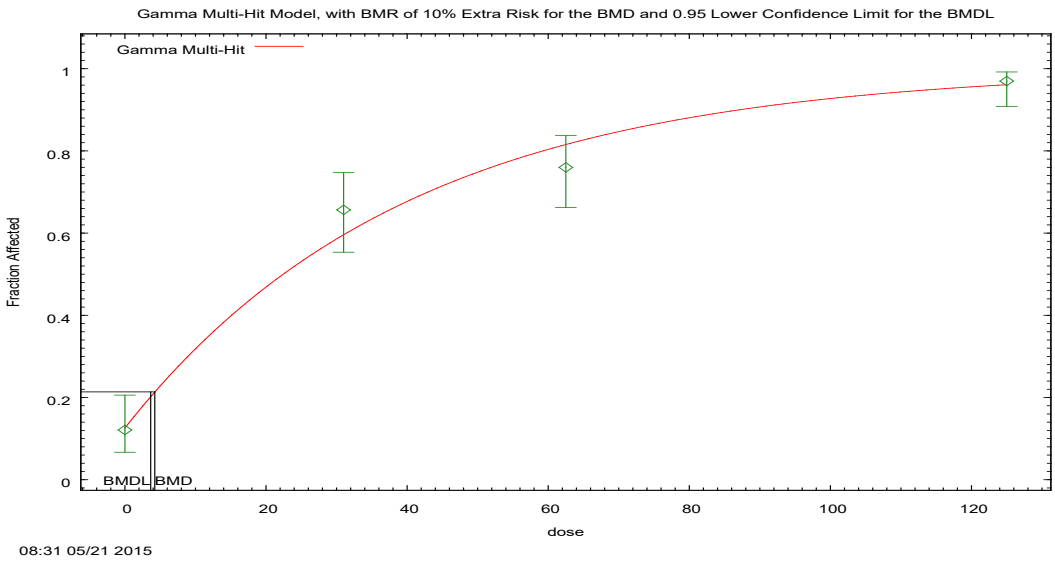

Figure 3 Incidence Rate by Dose for Rat Respiratory EPI, Hyperplasia

Gamma Model. (Version: 2.16; Date: 2/28/2013)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 4.23277

BMDL at the 95% confidence level = 3.6578

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.126482	0.128713
Slope	0.0248916	0.0379463
Power	1	1.3

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-168.83	4			
Fitted model	-170.68	2	3.703	2	0.16
Reduced model	-262.65	1	187.647	3	<.0001

AIC: = 345.366

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1265	12.522	12	99	-0.16
31	0.5962	59.025	65	99	1.22
62.5	0.8157	81.566	76	100	-1.44
125	0.9611	96.11	97	100	0.46

Chi^2 = 3.79 d.f = 2 P-value = 0.15

D.4 BMDS Summary of Rat Respiratory EPI Metaplasia Squamous

Table 22 Summary of BMD Modeling Results for Rat Respiratory EPI Metaplasia squamous

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	0.397	243.57	62.3	51.4
Dichotomous-Hill LogLogistic	0.469	243.37	62.1	51.8
Logistic	**0.981**	**240.90**	**61.5**	**54.1**
Probit	0.575	241.78	57.2	50.1
LogProbit	0.337	243.80	63.2	53.1
Weibull	0.613	243.11	61.5	50.9
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.811	241.29	58.8	50.3
Multistage 2°	0.0134	250.37	44.2	40.0
Quantal-Linear	0	285.38	22.9	19.0

[a] Selected model in bold; scaled residuals for selected model for doses 0, 31, 62.5, and 125 were 0.18, -0.06, -0.05, 0.02, respectively. Basis for model selection is the lowest AIC

[b] BMD or BMDL computation failed for this model.

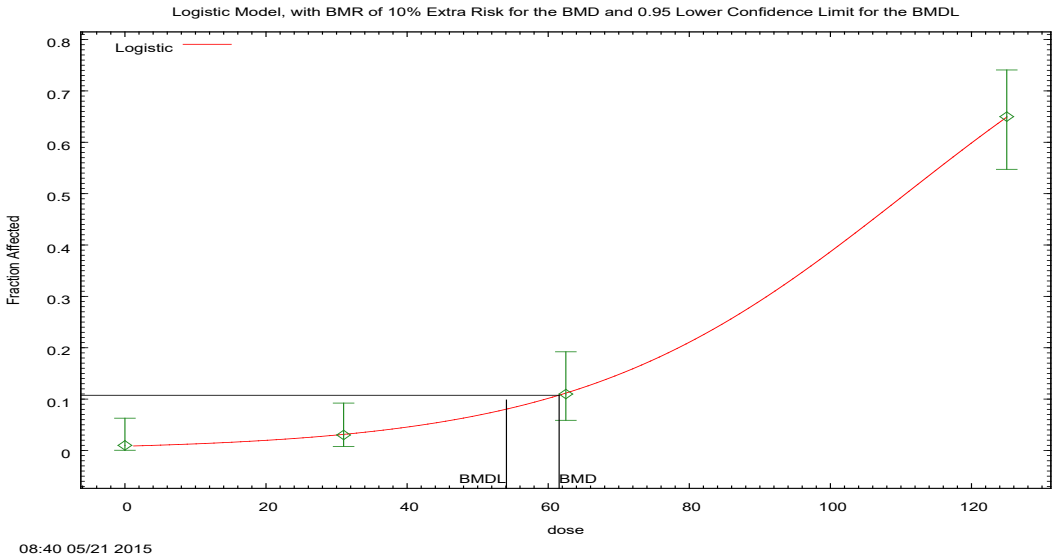

Figure 4 Incidence Rate by Dose for Rat Respiratory EPI Metaplasia Squamous

Logistic Model. (Version: 2.14; Date: 2/28/2013)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]
Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk
BMD = 61.5482
BMDL at the 95% confidence level = 54.0805

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-4.7630E+00	-4.3667E+00
slope	0.0430184	0.0390209

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-118.43	4			
Fitted model	-118.45	2	0.0366578	2	0.98
Reduced model	-199.71	1	162.567	3	<.0001

AIC: = 240.896

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0085	0.838	1	99	0.18
31	0.0314	3.107	3	99	-0.06
62.5	0.1116	11.162	11	100	-0.05
125	0.6489	64.892	65	100	0.02

Chi^2 = 0.04 d.f = 2 P-value = 0.981

Appendix E Benchmark Concentration Modeling for Mouse Data

E.1 BMDS Summary of Mouse Olfactory EPI Atrophy

Table 23 Summary of BMD Modeling Results for Mouse Olfactory EPI Atrophy

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	1.000	245.53	11.9	9.95
Dichotomous-Hill LogLogistic	0.940	245.54	12.7	11.1
Logistic	0.0015	258.83	4.44	3.72
Probit	0.0027	256.92	4.02	3.45
LogProbit	0.996	245.53	12.4	10.8
Weibull	1.000	245.53	10.2	8.15
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	**0.746**	**244.16**	**9.30**	**6.08**
Multistage 2°	0.0125	254.09	6.08	4.89
Quantal-Linear	0	283.51	1.65	1.41

[a] Selected model in bold; scaled residuals for selected model for doses 0, 16, 31, and 62.5 were 0.19, -0.52, 0.53, 0, respectively. Basis for model selection is the lowest AIC

[b] BMD or BMDL computation failed for this model.

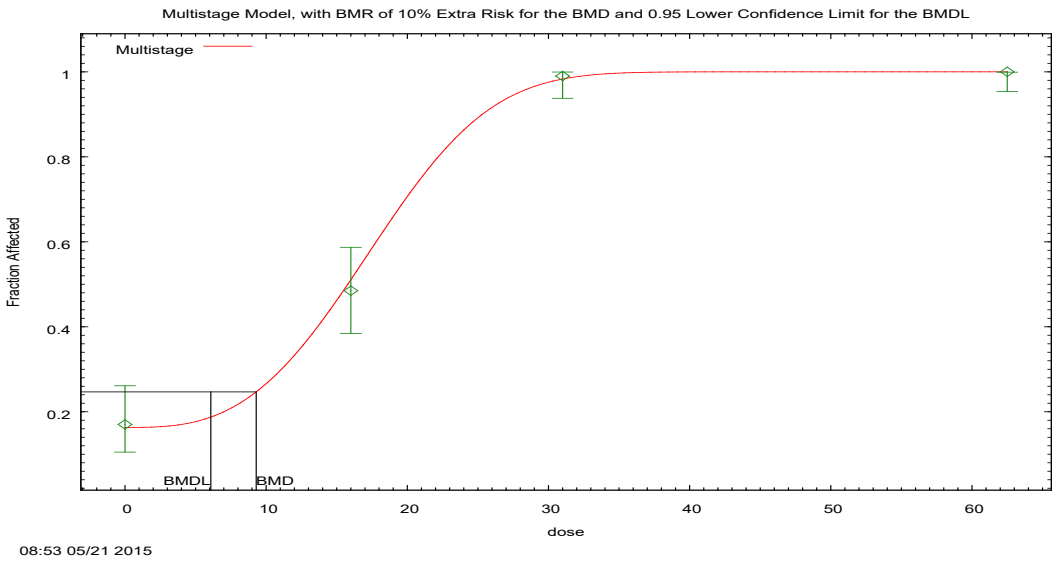

Figure 5 Incidence Rate by Dose Mouse Olfactory EPI Atrophy

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 9.29566

BMDL at the 95% confidence level = 6.08026

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.162917	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.000131171	4.2403E+14

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-119.76	4			
Fitted model	-120.08	2	0.632618	2	0.73
Reduced model	-255.33	1	271.136	3	<.0001

AIC: = 244.162

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1629	16.292	17	100	0.19
16	0.5109	50.575	48	99	-0.52
31	0.9832	98.319	99	100	0.53
62.5	1	100	100	100	0

Chi^2 = 0.59 d.f = 2 P-value = 0.7461

E.2 BMDS Summary of Mouse Olfactory EPI Respiratory Metaplasia

Table 24 Summary of BMD Modeling Results for Mouse Olfactory EPI Respiratory Metaplasia

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	**0.935**	**299.94**	**17.1**	**14.3**
Dichotomous-Hill	0.871	301.85	18.9	15.3
Logistic	0	333.62	4.91	4.25
LogLogistic	0.871	301.85	18.9	14.5
Probit	0	332.15	4.61	4.05
LogProbit	0.987	301.80	18.1	14.5
Weibull	1.000	301.80	19.2	13.8
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.0291	307.07	11.8	10.1
Multistage 2°	0	321.73	7.99	6.92
Quantal-Linear	0	362.19	2.40	2.04

[a] Selected model in bold; scaled residuals for selected model for doses 0, 16, 31, and 62.5 were 0.23, -0.28, 0.08, 0.01, respectively. Basis for model selection is the lowest AIC

[b] BMD or BMDL computation failed for this model.

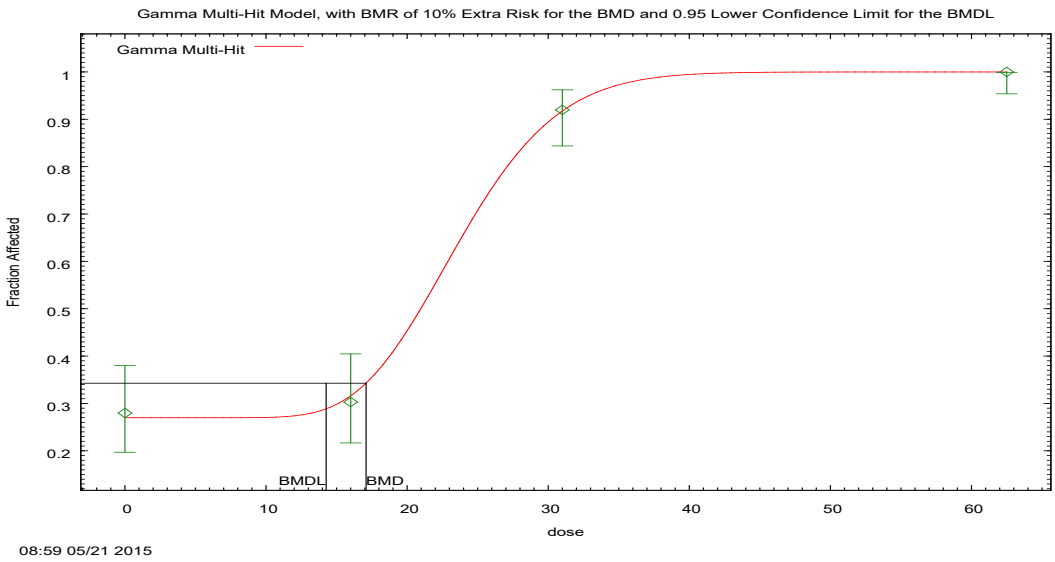

Figure 6 Incidence Rate by Dose for Mouse Olfactory EPI Respiratory Metaplasia

Gamma Model. (Version: 2.16; Date: 2/28/2013)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 17.0917

BMDL at the 95% confidence level = 14.2611

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.26982	0.284314
Slope	0.750166	0.158982
Power	18	4.20781

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-147.9	4			
Fitted model	-147.97	2	0.135511	2	0.93
Reduced model	-263.64	1	231.485	3	<.0001

AIC: = 299.935

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.2698	26.982	28	100	0.23
16	0.3159	31.271	30	99	-0.28
31	0.9177	91.769	92	100	0.08
62.5	1	100	100	100	0.01

Chi^2 = 0.14 d.f = 2 P-value = 0.9346

E.3 BMDS Summary of Mouse Respiratory EPI Metaplasia Squamous

Table 25 Summary of BMD Modeling Results for Mouse Respiratory EPI Metaplasia Squamous

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	0.419	335.09	20.8	16.5
Dichotomous-Hill	N/A[b]	336.42	22.3	17.2
Logistic	0.235	335.41	20.4	17.9
LogLogistic	0.481	334.93	20.9	16.8
Probit	0.296	334.99	18.9	16.6
LogProbit	0.731	334.54	21.3	17.3
Weibull	0.247	335.81	20.1	15.7
Multistage 4°	error	error	error[c]	error[c]
Multistage 3°	0.232	335.92	19.6	15.3
Multistage 2°	**0.480**	**333.99**	**19.0**	**15.3**
Quantal-Linear	0	355.33	8.36	7.05

[a] Selected model in bold; scaled residuals for selected model for doses 0, 16, 31, and 62.5 were 0.41, -1.03, 0.48, 0.01, respectively. Basis for model selection is the lowest AIC
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.

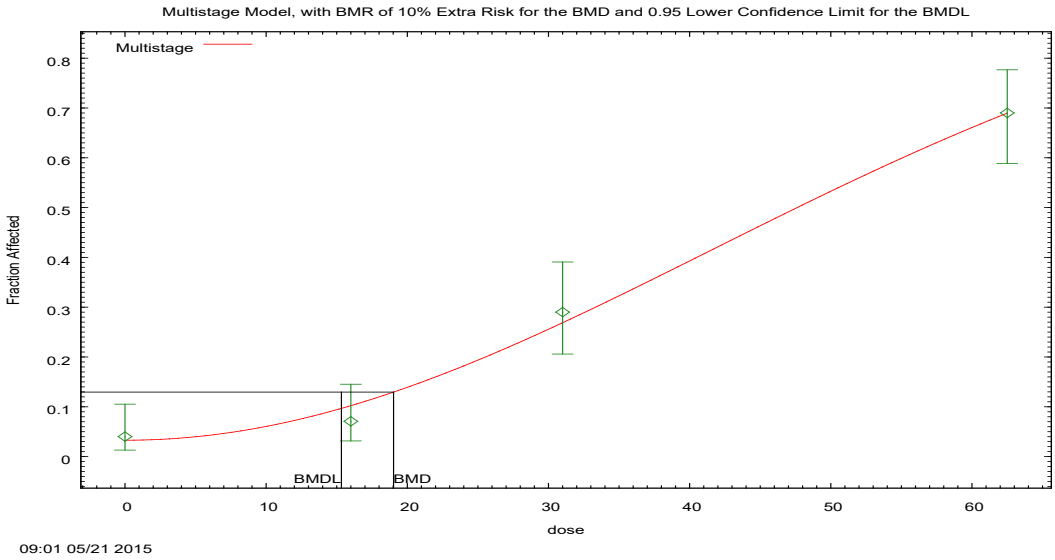

Figure 7 Incidence Rate by Dose for Mouse Respiratory EPI Metaplasia Squamous

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 19.0258

BMDL at the 95% confidence level = 15.3313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0326591	0.0279972
Beta(1)	0	0.000359559
Beta(2)	0.000291068	0.000287877

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-164.21	4			
Fitted model	-164.99	2	1.56768	2	0.46
Reduced model	-233.97	1	139.525	3	<.0001

AIC: = 333.989

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0327	3.266	4	100	0.41
16	0.1021	10.11	7	99	-1.03
31	0.2687	26.869	29	100	0.48
62.5	0.6897	68.969	69	100	0.01

Chi^2 = 1.47 d.f = 2 P-value = 0.4802

E.4 BMDS Summary of Mouse Turbinate Hyperostosis

Table 26 Summary of BMD Modeling Results for Mouse Turbinate Hyperostosis

Model[a]	Goodness of fit *p*-value	Goodness of fit AIC	BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)
Gamma	0.999	214.46	11.5	9.65
Dichotomous-Hill LogLogistic	0.939	214.47	12.5	10.9
Logistic	0.0191	221.42	5.92	4.84
Probit	0.0239	220.76	5.11	4.27
LogProbit	0.995	214.46	12.1	10.6
Weibull	1.000	214.46	9.71	7.82
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	**0.866**	**212.76**	**9.13**	**5.71**
Multistage 2°	0.0169	222.45	5.99	4.85
Quantal-Linear	0	253.19	1.61	1.39

[a] Selected model in bold; scaled residuals for selected model for doses 0, 16, 31, and 62.5 were 0.1, -0.35, 0.4, 0, respectively. Basis for model selection is the lowest AIC

[b] BMD or BMDL computation failed for this model.

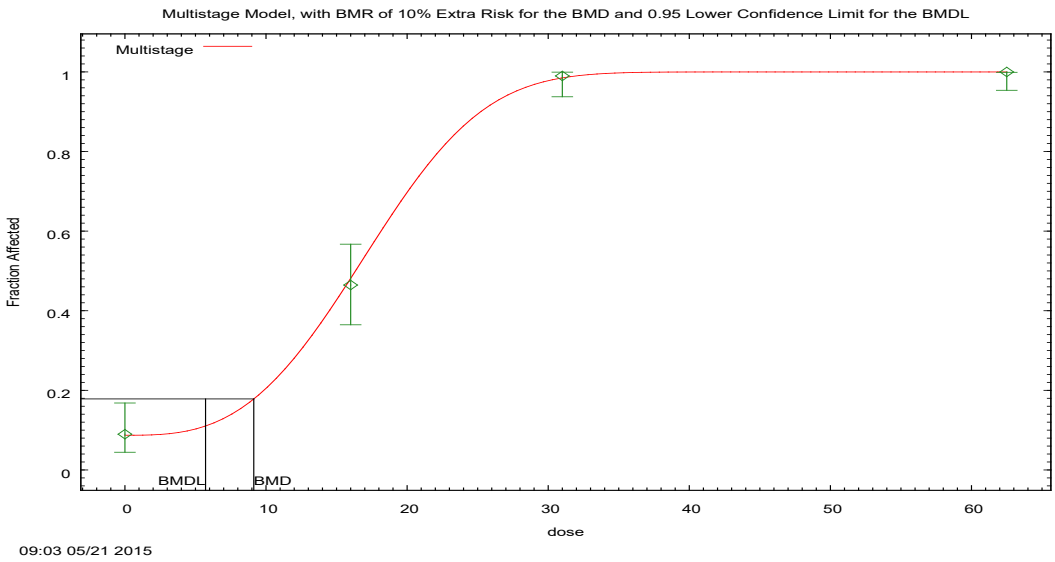

Figure 8 Incidence Rate by Dose for Mouse Turbinate Hyperostosis

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 9.13336

BMDL at the 95% confidence level = 5.71461

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0873147	0
Beta(1)	0	0
Beta(2)	0	0

Beta(3)	0.000138288	4.2403E+14

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-104.23	4			
Fitted model	-104.38	2	0.308813	2	0.86
Reduced model	-261.49	1	314.517	3	<.0001

AIC: = 212.764

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0873	8.731	9	100	0.1
16	0.482	47.719	46	99	-0.35
31	0.9852	98.517	99	100	0.4
62.5	1	100	100	100	0

Chi^2 = 0.29 d.f = 2 P-value = 0.8658

Appendix F Review of Genetic and Carcinogenicity Toxicity Studies (NTP 2011)

(Reproduced directly from NTP (2011))

Genetic Toxicity

Published data provide no evidence of diethylamine-associated genotoxicity, although data from mammalian cell studies are limited. The genetic toxicity of diethylamine has been investigated in several prokaryotic systems. Incubation with diethylamine (140 mg/L; 1,900 mM) for 1 hour in the absence of metabolic activation did not induce the lambda prophage in *Escherichia coli* strain K-12 (Thomson and Woods, 1975). Several studies reported that diethylamine was not mutagenic in *Salmonella typhimurium*. Cotruvo *et al.* (1978) first concluded that neither diethylamine (220 μmol/plate) nor ozonated diethylamine (ozonated in water for 1 hour at pH 11.1) induced gene mutations in *S. typhimurium*; testing was conducted in strains TA98, TA100, TA1535, TA1536, TA1537, and TA1538 with and without rat liver S9. Zeiger *et al.* (1987) exposed *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 to a dose range of 33 to 3,333 μg/plate (0.5 to 46 μmol/plate) using the preincubation method in either the presence or absence of 10% induced rat or hamster liver metabolic enzymes (Appendix E); no increases in revertant colonies were observed with any strain or activation condition at any dose level of diethylamine. Similarly, diethylamine did not induce *his* gene mutations in *S. typhymurium* strains TA98, TA100, or TA1538 using the plate incorporation method in either the presence or absence of rat liver S9 (Khudoley *et al.*, 1987).

The potential ability of diethylamine to cause DNA damage in an *in vivo* mammalian test system was investigated by Loury *et al.* (1987). Male F344/N rats were administered 500 mg/kg diethylamine by gavage, and when evaluated 12 hours later, there was no evidence of unscheduled DNA synthesis in their kidney cells.

Carcinogenicity

Experimental Animals

No studies evaluating the carcinogenicity of diethylamine or other aliphatic amines were found in the literature. Diethylamine is the only aliphatic amine evaluated in a chronic carcinogenicity study by the NTP.

Because dietary amines can potentially react with salivary nitrite to produce carcinogenic nitrosamines, the coadministration of diethylamine and sodium nitrite has been investigated in several studies. Galea et al. (1975) treated Wistar rats with sodium nitrite (15 mg/day) and diethylamine (15 mg/day) in the diet for up to 217 days. Hyperplasia of Kupffer cells, small periportal inflammatory infiltrates, and chronic interstitial nephritis were observed in treated rats. Nitrosodiethylamine was not detected in the stomachs of treated rats.

There were no significant increases in the incidences of liver neoplasms in male C57 × C3H mice administered a single 50 mg/kg dose of diethylamine hydrochloride by gavage on postnatal day 15 and held for 110 wks after treatment (Rijhsinghani et al., 1982). However, when diethylamine treatment was followed by a single 50 mg/kg dose of sodium nitrite, there was a significant increase in the incidence of liver tumors compared to that in mice administered diethylamine hydrochloride alone. In a three-generation reproductive toxicity study, F0 rats were administered sodium nitrite (100 mg/kg; 1,000 μmol/kg) in drinking water beginning at 30 days of age (Druckrey et al., 1963). The F1 and F2 offspring of these rats were given either sodium nitrite (100 mg/kg) in drinking water and diethylamine hydrochloride (500 mg/kg in feed) concurrently or sodium nitrite (100 mg/kg) alone in drinking water for life. No treatment-related effects were reported.

No liver neoplasms were detected in male English short-hair guinea pigs after administration of 4.0 g/L diethylamine hydrochloride in drinking water for 2.5 years or after concurrent administration of diethylamine hydrochloride and sodium nitrite (Sen et al., 1975). Treated animals receiving both chemicals were administered either a low mix consisting of 2.0 g/L diethylamine hydrochloride plus 0.4 g/L sodium nitrite for 2.5 years or a high mix consisting of 4.0 g/L diethylamine hydrochloride plus 0.8 g/L sodium nitrite for 18 months after which plain water was given for 12 months.

Humans

No epidemiology studies or case reports examining diethylamine exposure and cancer risk in humans were found in the literature.