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Diisopropylamine

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Prepared by

Roberta L. Grant, Ph.D.

Jong-Song Lee, Ph.D.

Pallavi Kompella

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
°C	degrees Celsius
BMR	benchmark response
BW	body weight
DSD	development support document
ECHA	European Chemicals Agency
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
ET	extrathoracic
F	female
h	hour(s)
HEC	human equivalent concentration

Acronyms and Abbreviations	Definition
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
LC_{50}	The concentration required to kill half the members of a tested population after specified test duration
M	male
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)
MOA	mode of action
n	number
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OECD	Organisation for Economic Co‑operation and Development
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

Acronyms and Abbreviations	Definition
RD_{50}	50% reduction in respiration rate
$RD_{50}TC$	concentration of irritant leading to 50% reduction in respiration rate
RGDR	regional gas dose ratio
ReV	reference value
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)

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of diisopropylamine (DIPA). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015a) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on DIPA's physical/chemical data.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV [1 h]	870 µg/m^3 (210 ppb) **Short-Term Health**	**Critical Effect(s)**: Histological changes in anterior respiratory epithelium and olfactory epithelium in mice
$^{acute}ESL_{odor}$	540 µg/m^3 (130 ppb) **Odor**	ammonia or fish-like odor
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	18 µg/m^3 (4.3 ppb) **Long-Term Health**	**Critical Effect(s)**: Surrogated to dibutylamine (DBA, decreased body weight). Because of limited toxicity data, a category/read across approach was used to determine a chronic ReV based on DBA's $^{chronic}ESL_{threshold(nc)}$.
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Inadequate information to assess carcinogenic potential via the inhalation pathway
$^{chronic}ESL_{veg}$	- - -	No data found

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

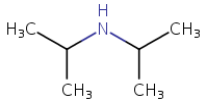
Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	260 µg/m^3 (63 ppb)[a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s)**: Corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates in rats
$^{acute}ESL_{odor}$	**540 µg/m^3 (130 ppb)**	ammonia or fish-like odor
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL$	5.4 µg/m^3 (1.3 ppb)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s)**: Surrogated to dibutylamine (DBA, decreased body weight). Because of limited toxicity data, a category/read across approach was used to determine a chronic ReV based on DBA's $^{chronic}ESL_{threshold(nc)}$.
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Inadequate information to assess carcinogenic potential via the inhalation pathway.
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Based on the acute ReV of 870 µg/m^3 (210 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on DBA's $^{chronic}ESL_{threshold(nc)}$

Table 3 Chemical and Physical Data for Diisopropylamine

Parameter	Values for DIPA	Reference
Molecular Formula	$C_6H_{15}N$	HSDB (2014)
Chemical Structure		ChemIDPlus
Molecular Weight ($gmol^{-1}$)	101.191	NIOSH (2011)
Physical State at 25°C	Liquid	NIOSH (2011)
Color	Colorless	NIOSH (2011)
Odor	ammonia or fish-like odor	NIOSH (2011)
CAS Registry Number	108-18-9	NIOSH (2011)
Synonyms	DIPA, N-(1-Methylethyl)-2-propanamine	NIOSH (2011)
Solubility in water	110 g/L at 25°C	HSDB (2014)
Log Kow	1.4	HSDB (2014)
pKa	11.07	HSDB (2014)
Density (water = 1)	0.7169	HSDB (2014)
Vapor Pressure	79.4 mm Hg at 25 °C	HSDB (2014)
Melting Point	-61 °C	HSDB (2014)
Boiling Point	84°C	HSDB (2014)
Conversion Factors	1 ppm = 4.14 mg/m^3; 1 mg/m^3 = 0.24 ppm	NIOSH (2011)

Chapter 2 Major Sources and Uses

DIPA is a secondary amine, which is used as a chemical intermediate, and catalyst for the synthesis of pesticides and pharmaceuticals. DIPA is primarily used as a precursor for the herbicides dilate and triallate, as well as certain sulfenamides used in the vulcanization of rubber (Eller et al. 2000). It is used for adjusting pH in cosmetic formulations, in colognes, and toilet cleaners (Pang 1995). DIPA is commercially available. It is associated with tobacco either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products (NTP 2015).

When given intravenously to hypertensive patients, DIPA is known as an antihypertensive agent. DIPA exerts its action by lowering arterial blood pressure, reduction of stroke volume and cardiac output (Schwarz 1974). Polacek and Breuer (1978) observed DIPA reduced blood glucose concentrations in fasted mice and in fasted, glucose-loaded, or streptozotocin-diabetic rats.

The Organisation for Economic Co‑operation and Development (OECD 2013) reports that less than 227 tons were produced in the United States in 2006. DIPA 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 to assess DIPA concentrations in Texas ambient air.

Chapter 3 Acute Evaluation

A committee of the Health Council of Netherlands (2003) reassessed the administrative occupational exposure limits for DIPA and Pang (1995) reviewed the safety of DIPA for use in cosmetic ingredients. OECD (2013) grouped DIPA in their aliphatic secondary amine group in their SIDS Initial Assessment Profile, which provides a summary review of the toxicity of DIPA. The TCEQ reviewed the toxicity information in these documents, but also conducted a thorough review of the scientific literature.

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

3.1.1 Physical/Chemical Properties

DIPA is a secondary amine and is a colorless liquid at room temperature with a fishy, ammonia-like odor (NIOSH 2011). It is strongly alkaline with a pKa of 11.07 (ACGIH 1999; HSDB 2014). It has a molecular weight of 101.91 g mol^{-1} and a vapor pressure of 70 mm Hg at 20 ºC (NIOSH 2011). If released to air, DIPA will exist solely in the vapor phase in the ambient atmosphere.

DIPA is flammable and incompatible with strong oxidizing agents. DIPA may react violently with strong acids or oxidizers (NIOSH 2011). DIPA is soluble in water as well as in acetone,

benzene, ether, and ethanol (HSDB 2014) and has a log K_{ow} of 1.4 (HSDB 2014). Other physical/chemical properties of DIPA can be found in Table 3 above.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

Inhalation of sufficiency high DIPA vapor concentrations for a sufficient duration causes irritation, sometimes with nausea and vomiting and can also cause burns to the respiratory system. Amine vapors may lead to edema of the corneal epithelium, although exposed workers generally do not report pain (Grant 1986). High concentrations on the skin caused pain and first-degree burns on short-term exposure and may cause second-degree burns on long-term exposure (HSDB 2014).

Men engaged in the distillation of DIPA in a pilot plant operation reported cases of transient dimness of vision and in a few instances, nausea, and headaches (Treon et al. 1949). Visual distress occurred within two to three hours (h) after exposure to unusually high concentrations of the vapor. The visual effects persisted for 1 to 2 h after the men went out into fresh air. The mean concentration of DIPA in the pilot plant was said to be of the order of 100 to 200 mg/m^3 (24-48 ppm), with 5 to 10-minute (min) peaks of about 740 mg/m^3 (178 ppm), occurring 2 or 3 times daily, near a drum into which DIPA was being drained. Based on these reported human cases, Treon et al. (1949) conducted studies in animals, as described in Section 3.1.2.2.5. The findings in workers were not reliable and were not used to derive the acute reference value (ReV).

3.1.2.2 Animal Studies

In lethality, acute, and subacute inhalation studies, toxic effects were observed in the respiratory system and eyes of rabbits, rats, and guinea pigs. Table 4 summarizes various acute and subacute inhalation studies in animals arranged from low to high concentrations.

3.1.2.2.1 Key Animal Study (Zissu 1995)

Zissu (1995) conducted a study to investigate potential damage in the respiratory tract after mice were exposed at the RD_{50} (concentration of DIPA leading to a 50% reduction in respiration rate), 0.3 x RD_{50} and 3 x RD_{50}. Groups of male Swiss OF1 mice (10/group) were exposed in stainless steel inhalation chambers to 0 (control), 62 ± 11.5 ppm (0.3 x RD_{50}), 174 ± 29.3 ppm (RD_{50}), or 436 ± 89.7 ppm (3 x RD_{50}) DIPA [mean analytical concentrations ± S.D.] for 6 h/day (d), 5 d/week for 4, 9, or 14 d.

DIPA exposure produced marked excitation, rougher hair and a moderate decrease in body weight in exposed animals. DIPA induced severe histological changes in the nasal passages even at the lowest concentration of 62 ppm following 4-, 9-, and 14-d exposure. The anterior respiratory epithelium adjacent to the vestibule and the olfactory epithelium (slight loss of isolated sensory epithelium) were the principal sites affected. Rhinitis with metaplasia and

necrosis were observed in the respiratory epithelium lining (maxilloturbinates, the nasal turbinates, the septum and the lateral walls in the two proximal sections). As early as a 4-d exposure, lesions reached maximum severity. No histological differences were noted in the trachea and lungs of exposed animals compared to the control group. The lowest-observed-adverse-effect level (LOAEL) was 62 ppm for severe histopathology changes in the extrathoracic (ET) region. A no-observed-adverse-effect level (NOAEL) was not determined. The free-standing LOAEL (7 h/d for 4 d) of 62 ppm (257 mg/m^3) was used as a point-of-departure (POD) to derive the acute Rev and ESL.

3.1.2.2.2 Supporting Animal Studies

3.1.2.2.2.1 Thirty-Minute Lethality Study in Rats and Guinea Pigs

Price et al. (1979) conducted studies in rats and guinea pigs. Groups of 10 rats (5 males (M) and 5 females (F)) and 10 guinea pigs (5 M and 5 F) were exposed to 0 (control), 961, 1760, or 5120 ppm (0, 4,000, 7300, or 21,200 mg/m^3) DIPA vapor for 30 min. The rats were observed post exposure for 14 days. Necropsy was done either at time of death or at the end of the study.

After exposure to the highest concentration of 5120 ppm DIPA, all rats died from apparent respiratory distress. The rats had degeneration of the renal proximal tubular epithelium and bronchial epithelium, and the guinea pigs had vacuolar degeneration of the hepatocytes.

At 1760 ppm, two guinea pigs and one rat died either during or a few minutes after exposure. Signs of toxicity included nasal lachrymal irritation, which progressed to dyspnea, generalized depressed activity, and eyelid closure by 15 min. The body weights of the rats and the female guinea pigs were significantly lower than those of controls. The lung weights of the female guinea pigs and heart weights of the male rats were also significantly lower. One of the guinea pigs had congestion and exposure-related corneal erosion and edema, but the other guinea pig had no lesions. The rat had pulmonary congestion, inflammation, hemorrhage, and edema. Of the animals surviving the study, one guinea pig had corneal opacity 14 days after exposure. No other lesions were observed in the other animals.

At 961 ppm, deaths were not observed. Signs of toxicity included nasal lachrymal irritation, which progressed to dyspnea, generalized depressed activity, and eyelid closure by 15 min; these symptoms persisted for 4 h. Other significant changes were reduced body weights in female rats and increased lung weight of both rats and guinea pigs. No significant histopathological changes were found.

3.1.2.2.2.2 Two-Hour Lethality Studies

Greim et al. (1998) reported a 2-h LC_{50} value for DIPA of 4800 mg/m^3. No details on species or the study was reported. Two-hour LC_{50} values of 4800 mg/m^3 (1140 ppm) in rats and 4210 mg/m^3 (1000 ppm) in mice were reported by Izmerov et al. (1982). Details on the study are not available.

3.1.2.2.2.3 Four-Hour Lethality Study in Rats

Monsanto Co. (Long 1987) evaluated acute inhalation toxicity in three groups of 10 Sprague-Dawley (SD) rats (5/sex/group). The rats were exposed to DIPA at analytical concentrations of 0 (control), 5000, or 5300 mg/m^3 (0, 1200 or, 1270 ppm, respectively) for 4 h. The nominal/analytical concentration ratios were 1.7 and 1.4 for the mid and high dose groups respectively. DIPA concentration within the chambers was monitored by infrared spectroscopy at hourly intervals (four times per exposure).

Animals were observed for signs of toxicity immediately following exposure and on days 2, 7, and 14 post-exposure. Mortality checks were conducted twice daily. Body weights were recorded prior to exposure and on post-exposure days 2, 7, and 14. All rats were given a complete necropsy examination at death or following sacrifice on day 14.

Mortality was observed in one male rat on day 1 post exposure in the 5300 mg/m^3 group, however, no deaths occurred in the control group or in the 5000 mg/m^3 groups. All animals gained weight and exceeded their pre-exposure weights by post-exposure day 14 although there was an initial body weight decrease in most exposed animals on post-exposure day 2. Labored breathing, tremors, and high-pitched respiratory sounds were observed in animals immediately following exposure and during the 14-day post-exposure period. Signs of partially or completely closed eyes, nasal and ocular discharges and encrustation, ocular opacity, and pitted/raised corneal surface were also observed. Gross necropsy revealed corneal opacity. Based on the results, the approximate LC_{50} for both sexes was considered to be greater than 5300 mg/m^3.

Smyth et al. 1954 exposed a group of six male albino rats to saturated concentrations of DIPA (80000 ppm or 340000 mg/m^3). All of the rats died after 5 min. Two deaths occurred within 14 days of exposure when groups of six rats were exposed to 1000 ppm (4140 mg/m^3) DIPA for 4 h.

3.1.2.2.2.4 Lethality Studies in Different Species

Treon et al. (1949) conducted four experiments on various species of previously unexposed animals (rabbits, guinea pigs, rats, and cats). A disadvantage of this study is the use of only two animals per species, although it does provide information on the adverse inhalation effects of DIPA at different concentrations and species. Animals were exposed to DIPA vapor (whole body exposure) at various concentrations for varying periods of time (Experiment I: 2207 ppm for 3 h; Experiment II: 777 ppm for 7 h for 2 d; Experiment III: 597 ppm, 7 h/d for 7 d over a period of 9 d; and Experiment IV: 261 ppm, 7 h/d for 40 d over a period of 54 d. Concentrations were analytical determined.

- In Experiment I, all animals died within the 3-h exposure duration at 2207 ppm.
- In Experiment II, all animals (except one rabbit) survived after the 7-h exposure on the first day, all guinea pigs and the remaining rabbit died during the 6.33-h exposure on the following day at 777 ppm.

- In Experiment III, the rabbits, guinea pigs, and one rat died on the second, fourth, and fifth day of exposure at 597 ppm, respectively. The other rat and both cats survived throughout the entire exposure periods and were sacrificed within 2 months.
- In Experiment IV, 4 rabbits died on or before the 20^{th} day of exposure, one guinea pig died during its 19^{th} day of exposure at 261 ppm. The others survived throughout the entire 40 d of exposure.

Severe irritation of the respiratory mucus membranes were observed in all animals tested at various concentrations and duration. Some degree of corneal opacity of the eye also developed. The studies identified the lowest lethal concentration for the rabbits, guinea pigs, rats, and cats were 261 ppm, 261 ppm, 597 ppm, 2207 ppm, respectively. Thus, rabbits and guinea pigs were the most sensitive species among the animals tested.

3.1.2.2.2.5 Respiratory Depression Studies in Mice

The nasal sensory irritation produced by DIPA was studied using male Swiss OF_1 mice (Gagnaire et al.1993). Groups of six mice each were exposed to concentrations of DIPA (analytically determined) ranging from 88 to 351 ppm in air for 15 min. This study determined the concentration at which the respiratory rate was decreased by 50% (RD_{50}). The head of each mouse was isolated in an inhalation chamber, and the breathing frequency was measured with a pressure transducer before and during the exposure period. The RD_{50} for DIPA was found to be 161 ppm with maximal effects observed within 0.5 to 1 min.

Other groups of mice were exposed to 29 to 207 ppm of DIPA via tracheal cannulation for 120 min. The concentration that caused a 50% decrease in respiratory rate via this route ($RD_{50}TC$) was compared with the RD_{50} (161 ppm). The $RD_{50}TC$ was 102 ppm, and maximal effects were observed after 120 min of exposure. The $RD_{50}TC$/ RD_{50} ratio was 0.6 (i.e. less than 1), which indicates DIPA primarily caused lower airway effects.

Table 4 Summary of Lethality, Acute and Subacute Inhalation Studies

Species (n/sex)	Exposure Concentration	Exposure Duration	LOAEL [a]	Notes (References)
Occupational male workers	100-200 mg/m^3 average; 5-10 min peaks of 740 mg/m^3, 2-3 times/day	2-3 h	100 mg/m^3 (24 ppm)	Transient dimness of vision that persisted for 1-2 h (Treon et al. 1949)
Swiss OF1 mice (10M)	62, 174, 436 ppm	6h/d, 5d/week for 4, 9 or 14 d	62 ppm [b] (257 mg/m^3)	Severe histological changes in anterior respiratory epithelium and olfactory epithelium after 4 days of exposure (Zissu 1995)
Swiss OF1 mice (6 M)	88-351 ppm (inhalation) 29-207 ppm (tracheal cannulation)	15 min (inhalation) 120 min (tracheal cannulation)	RD_{50} 161 ppm (666 mg/m^3) $RD_{50}TC$ 102 ppm (422 mg/m^3)	Nasal and lower airway effects (Gagnaire et al. 1993)
SD rats (5M, 5F)	5000 and 5300 mg/m^3	4 h	5000 mg/m^3 (1200 ppm)	Labored breathing, tremors and high-pitched respiratory sounds; partially or completely closed eyes, nasal and ocular discharges and encrustation, ocular opacity, and pitted/raised corneal surface. Corneal opacity (Long 1987)
Rats & guinea pigs (5M, 5F)	961, 1760, 5120 ppm	30 min	961 ppm	Nasal lachrymal irritation, dyspnea, generalized depressed activity, eyelid closure; reduced body weights, and increased lung weight (Price et al. 1979)
Albino male rats	1000 ppm	4 h	1000 ppm	Two out of 6 deaths at 1000 ppm; all rats died at saturated concentrations (Smyth et al. 1954)
Groups of 2 Rats, guinea pigs, rabbits, and cats	2207 ppm for 3 h; 597 ppm,7 h/days for 7 days; 777 ppm for 7/d for 2 days; and 261 ppm, 7 h/days for 40 days	Various from 3 h to 7 h/d for 40 d	261 ppm [c] (rabbits and guinea pigs) 597 ppm (rats) 2207 ppm (cats)	Lowest lethal concentration. Animals showed severe irritation of the respiratory mucus membranes, corneal opacity of the eye (Treon et al. 1949)

[a] Free-standing LOAEL, no NOAEL was observed

[b] Key animal study

[c] Lowest lethal concentration (LCLo)

3.1.2.3 Reproductive/Developmental Studies

There were no short-term developmental toxicity studies conducted for DIPA. Twenty-eight-day and 1-month studies conducted in SD rats provided evidence that there were no adverse effects on reproductive organs when rats were exposed to DIPA (Section 4.1.3).

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

DIPA is a secondary aliphatic amine, which is strongly alkaline, with a pKa of 11.7 (HSDB 2014). 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. In RD_{50} studies conducted in mice, Gagnaire et al. (1993) observed that the power of different amines to irritate upper and deeper airways increases with increase in its lipophilic nature. DIPA is assumed to have a threshold MOA, which is relevant to humans. The default dose metric is the exposure concentration.

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

DIPA causes severe histological changes in respiratory and olfactory epithelium at a LOAEL of 62 ppm (257 mg/m^3) in mice after 4 days of exposure (Zissu 1995). The LOAEL is supported by a LOAEL of 24 ppm (100 mg/m^3) (hyperplasia and metaplasia of the nasal turbinates) in rats after a 30 d exposure (Roloff and Ruecker1987) (Section 4.1.2). Poorly reported findings in humans indicate 24 ppm (100 mg/m^3)(the lowest concentration reported) may cause transient dimness of vision and in a few instances nausea and headaches (Treon et al. 1949). Although the human findings were not reliable, using the lowest LOAEL of 62 ppm from a subacute rat study as the POD, ultimately along with applicable uncertainty factors, will protect against acute health effects reported in humans.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

The effects of DIPA are assumed to be concentration (C) and duration (T) dependent. However, the POD of 62 ppm, a free-standing LOAEL, is higher than a LOAEL of 24 ppm reported in occupational workers (Treon et al.1949) and the 30-day study in rats (Roloff and Ruecker 1987), and is close to the lowest lethality concentration (LCLo) of 261 ppm in rabbits and guinea pigs (Treon et al. 1949). Therefore, the POD of 6-h exposure duration was conservatively not adjusted to a POD_{ADJ} of 1-h exposure duration. The POD_{ADJ} is the POD of 62 ppm.

3.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

The key study was conducted in animals so the POD_{ADJ} was adjusted to the human equivalent point of departure (POD_{HEC}) using an animal-to-human dosimetric adjustment. DIPA produced nasal lesions. No animal to human toxicokinetic adjustments is necessary for nasal lesions since

absorption, distribution, metabolism, and excretion would be similar for point-of-entry (POE) effects. Since the critical effect for DIPA also occurred in the extrathoracic (ET) region, the dosimetric adjustment was conducted as a Category 1 vapor for adverse effects in the ET region.

The regional gas dose ratio in ET region ($RGDR_{ET}$) for vapors is equal to one (TCEQ 2015a). Therefore, the POD_{HEC} would be identical to the POD_{ADJ}. The resulting POD_{HEC} is equal to the POD_{ADJ} of 62 ppm.

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

The POD_{HEC} of 62 ppm was based on histological changes in anterior respiratory epithelium and olfactory epithelium in rats (Zissu 1995) and the critical effects are assumed to have a threshold MOA. 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 112.661 ppm; 10 for intra-species variability (UF_H), 3 for animal to human uncertainty (UF_A), 6 for the LOAEL to NOAEL uncertainty factor (UF_L) and 3 for the database uncertainty factor (UF_D) for a total UF of 900.

- 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 default dosimetric adjustment from animal-to-human exposure was conducted, which accounts for toxicokinetic differences but not toxicodynamic differences.
- a UF_L of 10 was used because the critical effect of DIPA at the concentration of 62 ppm (Zissu 1995) appears to be severe.
- a UF_D of 3 was used. There is an acute study in mice (Zissu 1995), a 30-d study in rats (Roloff and Ruecker 1987), and a poorly reported study in humans (Treon et al. 1949). Treon et al. (1949) also provided limited data on sensitivity across different species that indicated the differences were within a factor of 2 for rodents. Short-term developmental studies are not available for DIPA. Short-term developmental studies are not available for DIPA. However, collectively, the amine class has not been shown to cause reproductive/developmental effects (OECD 2013).

If three or more UFs are used for the acute ReV, and the cumulative UF exceeds 300, the TCEQ generally uses a maximum total UF of 300. This reduction from a higher cumulative UF is used in recognition of a lack of independence of these factors and to account for the interrelationships of uncertainty categories (TCEQ 2012). Therefore, DIPA's acute ReV is calculated as follows:

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$

= 62 ppm⁄(10 x 3 x 6 x 3)
= 62 ppm⁄300
= 0.207 ppm x 1000 ppb/ppm
= 210 ppb (rounded to two-significant figures)

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

The acute ReV was rounded to two significant figures. The resulting 1-h acute ReV is 210 ppb (870 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 260 µg/m^3 (63 ppb) (Table 5).

3.2 Odor Perception

DIPA has a characteristic fishy, ammonia-like odor (HSDB 2014). Odor thresholds of 0.5 to 7.6 mg/m^3 (0.1-1.8 ppm) have been reported (ACGIH 1999, Lundberg 1991). Iowa State University (2004) reported an odor threshold for DIPA of 3.5 ppb and a recognition threshold of 85 ppb (350 µg/m^3). Hellman and Small (1974) reported an odor detection, 50% odor recognition, and 100% odor recognition levels at 130, 380 and 850 ppb for DIPA, respectively. The ^{acute}ESL$_{odor}$ for DIPA, based on an evidence-integration approach (TCEQ 2015b) is 130 ppb (540 µg/m^3).

3.3 Vegetation Effects

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

3.4 Short-Term ESL

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

- acute ReV = 870 µg/m^3 (210 ppb)
- ^{acute}ESL = 260 µg/m^3 (63 ppb)
- ^{acute}ESL$_{odor}$ = 540 µg/m^3 (130 ppb)

The short-term ESL for air permit evaluations is the ^{acute}ESL of 260 µg/m^3 (63 ppb) (Table 2).

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

Parameter	**Summary**
Study	Zissu (1995)
Study population	Male Swiss $OF_{1,}$ 10 M per group
Study quality	Medium
Exposure Method	Whole body exposure to DIPA vapor
Exposure Concentrations	0 (control), 62, 174, 436 ppm (analytical)
Exposure duration	6 h/d, for 4 d
Critical effects	Histological changes in anterior respiratory epithelium and olfactory epithelium after 4 days of exposure
LOAEL	62 ppm (free-standing)
NOAEL	Not available
POD_{ADJ} (1 h)	62 ppm
POD_{HEC}	62 ppm
Total UFs	900 (default to 300)
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	10
Incomplete Database UF *Database Completeness*	3 Low - Medium
acute ReV [1 h] (HQ = 1)	**870 µg/m^3 (210 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**260 µg/m^3 (63ppb)**

3.5 Acute Inhalation Observed Adverse Effect Level

The $LOAEL_{HEC}$ value of 62 ppm determined in mice rats from Zissu (1995) (Table 6) was 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. Animal-to-human dosimetric adjustments were conducted to derive the $LOAEL_{HEC}$ of 62 ppm (100 mg/m^3). Duration adjustments were not applied (TCEQ 2015).

The $LOAEL_{HEC}$ determined from animal studies represents a concentration at which 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. The effects are not a certainty due to potential intra-species differences in sensitivity. The acute inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2015a).

Chapter 4 Chronic Evaluation

A committee of the Health Council of Netherlands (2003) reassessed the administrative occupational exposure limits for DIPA and Pang (1995) reviewed the safety of DIPA for use in cosmetic ingredients. OECD (2013) grouped DIPA in their aliphatic secondary amine group in their SIDS Initial Assessment Profile. OECD (2013) only provides a summary review of the toxicity of DIPA. The TCEQ reviewed the toxicity information in these documents, but also conducted a thorough review of the scientific literature.

4.1 Non-Carcinogenic Potential

Chemical-specific chronic toxicity data from human studies are not available for DIPA. There is one 30-d study in rats (Roloff and Ruecker 1987) available, but no subchronic or chronic-duration animal studies. The identified free-standing LOAEL from Roloff and Ruecker (1987) was used to derive a chronic ReV. Since there is uncertainty in using a 30-d rodent study (the cutoff between a subacute and subchronic study) to develop a chronic ReV, a relative potency factor (RPF) approach was investigated using dibutylamine (DBA) as the index chemical (Appendix A), and a category/read-across approach for reviewing toxicity of DIPA, DBA and diethylamine (DEA) (Appendix B) was also conducted in consideration of setting a generic long-term ESL for DIPA. These approaches are also associated with uncertainties. A weight of evidence approach was ultimately used to determine the most defensible chronic toxicity factors using these different approaches.

4.1.1 Physical/Chemical Properties

Like DBA and DEA (TCEQ 2015c, 2015d), DIPA has high pKa value (11.07) (HSDB 2014) that indicates it is corrosive. DIPA is soluble in water as well as organic solvents. For other physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.2 Key Study - Roloff and Ruecker (1987)

Monsanto Company conducted a one-month repeat concentration toxicity study of DIPA in Sprague Dawley (SD) rats (Roloff and Ruecker 1987). Groups of male and female SD rats (15/sex/group) were exposed 6 h/d, 5 d/week for 1 month whole-body to DIPA vapor at concentrations of 0 (control), 100 ± 0.0, 600 ± 10, or 2000 ± 10 mg/m^3. This study was

conducted using GLP and a protocol similar to OECD Guideline 412. European Chemicals Agency (ECHA 2015) considered this study reliable without restriction.

At 2000 mg/m^3, one male and 2 female rat died during the study. Signs of toxicity included respiratory difficulties, mucous membrane irritation, and non-responsiveness. At necropsy, changes in organ weights found in the exposed animals included increased relative adrenal gland, heart, and kidney weights and decreased relative spleen weights in males and females, and increased relative liver weights in females. The body weights were statistically lower than those of the control group throughout the study by 41%. Corneal lesions were observed in 100% of the animals. Almost all rats exposed to 2000 mg/m^3 also had lesions in the trachea (mucosal epithelial hyperplasia/metaplasia; inflammation) and in the lungs (bronchiolar epithelial hyperplasia/metaplasia). Erythrocyte count, hemoglobin, and hematocrit values were statistically increased (9-11%) in the male and female rats at 2000 mg/m^3.

At 600 mg/m^3, no animals died. The body weights of animals exposed to 600 mg/m^3 were statistically lower than those of the control group throughout the study by 10% and corneal lesions were observed in 75% of the animals. Erythrocyte count, hemoglobin, and hematocrit values were increased in female rats at 600 mg/m^3. All rats exposed to 600 mg/m^3 had hyperplasia and metaplasia of the nasal turbinates. Inflammation, mucosal erosion/ulceration, and necrosis/dissolution of turbinate septal cartilage or bone were also observed in most of the animals exposed to 600 mg/m^3.

At 100 mg/m^3, no animals died. Most of the rats exposed to 100 mg/m^3 had hyperplasia and metaplasia of the nasal turbinates. Corneal lesions were observed in 13% of the animals of the low dose group.

Summary of Findings
The body weights of animals in the mid- and high-dose groups were statistically lower than those of the control group throughout the study. Corneal lesions were observed in 13, 75, and 100% of the rats exposed to low-, mid-, and high-dose group. All rats exposed to 600 or 2000 mg/m^3 and most of the rats to 100 mg/m^3 had hyperplasia and metaplasia of the nasal turbinates. All treated male rats in the high-, mid-, and low-dose groups had reduced leukocyte counts due to reductions in lymphocytes (Table 6). Table 7 provides details of adverse changes in the nose and turbinates.

Table 6 Group Means of Hematology Data Significantly Different from Controls

	0 (control)	100 mg/m^3	600 mg/m^3	2000 mg/m^3
White blood cells	10.0	7.8 **	7.8 **	7.2 **
Absolute Lymphocytes	9.23	6.10 **	6.80 **	6.02 **

** Dunnett's T is significant at the 0.99 level

Table 7 Incidence of Microscopic Findings in the Nose/Turbinates

	Sex (n=15)	0 (control)	100 mg/m^3	600 mg/m^3	2000 mg/m^3
Inflammation	M	0	1	14 **	15 **
Inflammation	F	0	1	12 **	15 **
Hyperplasia/metaplasia Mucosal epithelium	M	0	12 **	15 **	15 **
Hyperplasia/metaplasia Mucosal epithelium	F	0	14 **	15 **	15 **
Necrosis/dissolution, turbinate/septum cartilage/bone	M	0	0	10 **	15 **
Necrosis/dissolution, turbinate/septum cartilage/bone	F	0	0	10 **	15 **

** Significantly different ($p \leq 0.01$) from control using Fisher's exact test with the Bonferroni inequality

The free-standing LOAEL for this 30-d exposure study was 100 mg/m^3 for the following critical effects: corneal lesions in 13% of the animals; reduced leukocyte counts in all treated males; and hyperplasia and metaplasia of the nasal turbinates in most rats. A NOAEL was not determined.

4.1.3 Reproductive/Developmental Studies

Subchronic studies conducted in SD rats provided evidence that there were no adverse effects on reproductive organs when rats were exposed to DIPA. Table 8 provides summary information on three repeat-dose studies that were conducted in accordance with the OECD guidelines (studies described in ECHA 2015).

Table 8 Summary of Studies that Evaluated Reproductive Organs

Animal species / Sex	Type of study / Year	Guidelines	Route / Duration / Dose	Result
SD rats/ 15 M; 15 F	28-d Repeated Dose 1991	OECD 407	Oral daily for 4 weeks / 0, 15, 50 and 150 mg/kg bw/d	No effects were observed on mammary tissue, uterine cervix, ovaries, vagina, testes, seminal vesicles, prostate and epididymis (Study described in ECHA 2015)
SD rats/ 15 M; 15 F	1-month Repeated Dose 1987	OECD 412	Inhalation 6 h/d, 5 d/week for 1 month / 100, 600 and 2000 mg/m^3	No treatment-related effects were observed on uterus including the cervix, mammary glands, ovaries, testes with epididymides and seminal vesicles. (Roloff and Ruecker 1987; ECHA 2015)
SD rats/ 10 M; 10 F	1-month Repeated Dose 1987	OECD TG 410	Dermal / 5 times a week for 1 month / 0, 15, 50 and 150 mg/kg bw/d	No effects were observed on mammary tissue, uterine cervix, ovaries, uterine tubes, prostate, testes, and epididymis. (Heydens 1987; ECHA 2015)

4.1.4 Critical Effect and POD for the Key Study

DIPA causes corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates at a free-standing LOAEL of 100 mg/m^3 in rats after a one-month exposure (Roloff and Ruecker 1987). The 30-d LOAEL was used as POD to derive the chronic ReV.

4.1.5 MOA Analysis

DIPA is corrosive and strongly alkaline, with a pKa of 11.07. 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. DIPA is irritating to the skin and mucous membranes. The mechanism for severe pulmonary irritation observed in various species of animals was discussed by Treon (1949). The proposed mechanism is based on DIPA's strongly alkaline properties. This MOA indicates that the adverse effects observed are relevant to humans and have a threshold. The default dose metric is the exposure concentration.

4.1.6 Dosimetric Adjustments

4.1.6.1 Default Exposure Duration Adjustments

The effects of DIPA are assumed to be concentration and duration dependent. An adjustment from a discontinuous to continuous exposure duration was conducted (TCEQ 2015a) as follows:

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

where:

D = Exposure duration, h per day

F = Exposure frequency, days per week

POD_{ADJ} = 100 mg/m^3x (6/24) x (5/7) =17.86 mg/m^3

4.1.6.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

The key study was conducted in animals so the POD_{ADJ} was adjusted to the POD_{HEC} using an animal-to-human dosimetric adjustment. DIPA produced corneal lesions and this effect is considered a POE effect; therefore, adjustments for this endpoint were conducted as a Category 1 vapor for adverse effects in the ET region. DIPA also produced systemic (reduced leukocyte count) and respiratory effects (hyperplasia and metaplasia of the nasal turbinates), so adjustments were conducted as a Category 3 vapor for systemic effects.

For DIPA effects in the ET region, the $RGDR_{ET}$ region for vapors is equal to one (TCEQ 2015a). Therefore, as a category 1 vapors the POD_{HEC} would also be identical to the POD_{ADJ}. The resulting POD_{HEC} is equal to the POD_{ADJ} of 17.86 mg/m^3.

Considering DIPA as a Category 3 vapor, the POD_{ADJ} was adjusted to a POD_{HEC} using the following equation:

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

Since the measured blood/air partition coefficients in the rat ($(Hb/g)_A$) and human ($(Hb/g)_H$) for DIPA are not available, a default value of one is used as the DAF (i.e., $(H\ b/g)_A$/ $(H\ b/g)_H$) (TCEQ 2015a). The resulting subacute POD_{HEC} is equal to the POD_{ADJ} of 17.86 mg/m^3.

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

The POD_{HEC} of 17.86 mg/m^3 was based on corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates observed in rats (Roloff and Ruecker 1987) and these effects are assumed to have a threshold MOA. The default for threshold effects is to determine a POD and apply uncertainty factors (UFs) to derive a reference value (ReV). The

following UFs were applied to the POD_{HEC}; 10 for UF_H, 3 for UF_A, 3 for UF_L, 3 for a subchronic to chronic UF (UF_{Sub}) and 3 for UF_D, for a total UF of 2,700.

- 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 default dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences.
- a UF_L of 10 was used because the critical effect of DIPA at the free-standing LOAEL appears to be severe (Roloff and Ruecker 1987).
- a UF_{Sub} of 3 was considered adequate because although longer exposure could have produced a somewhat lower POD (e.g., the effects are assumed to be both concentration- and duration-dependent), DIPA has a log K_{ow} of 1.4 (HSDB 2014), which indicates it has little bioaccumulation potential (TCEQ 2015a).
- a UF_D of 3 was used because there is one subchronic study in rats (Roloff and Ruecker 1987), and there are three subchronic reproductive studies administered through oral/inhalation/dermal routes.

chronic ReV = $POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_{Sub} \times UF_D)$
= 17.86 mg/m^3 / (10 x 3 x 10 x 3 x 3)
= 17.86 mg/m^3 / 2,700
= 0.006615 mg/m^3 x 1000 µg/mg
= 6.6 µg/m^3 (rounded to two-significant figures)

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

The chronic ReV was rounded to two significant figures. The resulting ReV is 6.6 µg/m^3 (1.6 ppb). The rounded chronic ReV was then used to calculate the ^{chronic}ESL. At the target hazard quotient (HQ) of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 2 µg/m^3 (0.5 ppb) (Table 9). The quality of the study is medium and database completeness is medium to low. The derived chronic ReV and $^{chronic}ESL_{threshold(nc)}$ are likely biased low because a cumulative UF of 2,700 from five different UF categories was used to adjust the POD_{HEC}.

Table 9 Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	**Summary**
Study	Roloff and Ruecker (1987)
Study population	SD rats; 15 males and 15 females per group
Study quality	Medium
Exposure Method	Whole body exposure to DIPA vapor
Exposure Concentration	0 (control), 100, 600, or 2000 mg/m^3
Exposure duration	6 h/day, 5 days/week for 30 days
Critical effects	Corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates
LOAEL	100 mg/m^3 (free-standing)
NOAEL	Not available
POD_{ADJ}	17.86 mg/m^3
POD_{HEC}	17.86 mg/m^3
Total uncertainty factors (UFs)	2,700
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	10
Subchronic UF	3
Incomplete Database UF *Database Completeness*	3 Medium to low
Chronic ReV [1 h] (HQ = 1)	**6.6 µg/m^3 (1.6 ppb)**
$^{Chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**2 µg/m^3 (0.5 ppb**)

4.1.9 Chronic Generic ESLs ($^{chronic}ESL_{generic}$) for DIPA

4.1.9.1 Category/Read-Across Approach

The chronic ReV and ESL for DIPA are 18 and 5.4 µg/m^3, respectively, based on a category/read-across approach (OECD 2013) (Appendix A). DIPA, DBA and diethylamine (DEA) are structurally similar, and have similar physical/chemical properties (Table 10). The TCEQ derived a chronic ReV of 18 µg/m^3 (3.4 ppb) and 33 µg/m^3 (11 ppb) and a

$^{chronic}ESL_{threshold(nc)}$ of 5.4 and 9.9 µg/m^3 for DBA and DEA, respectively (TCEQ 2015c, 2015d). Based on the OECD read-across approach, the lowest chronic ReV and ESL of 18 and 5.4 µg/m^3 for DBA were selected as the chronic ReV and ESL for DIPA, respectively (Table 11).

4.1.9.2 Relative Potency Factor (RPF) Approach

The $^{chronic}ESL_{generic}$ for DIPA is 1.4 µg/m^3 based on a RPF approach using DBA as the index chemical (Appendix B). A RPF of 0.28 was calculated by a ratio of a 30-d LOAEL (24 ppm) for DIPA to a 30-d LOAEL (85 ppm) for DBA. The critical effects for both LOAELs are hyperplasia and metaplasia of the respiratory epithelium.

However, there is uncertainty in the calculated RPF because the exposure method for DIPA exposure was whole-body while for DBA exposure was nose only in rats. The RPF is likely biased low.

4.2 Carcinogenic Potential

4.2.1 Mutagenicity and Genotoxicity

The Health Council of the Netherlands provided this summary of mutagenicity and genotoxicity tests for DIPA.

> "Diisopropylamine (purity: 99%) was negative when adequately tested with and without metabolic activation systems from induced rat or hamster livers in a preincubation assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (dose range: 33-10,000 µg/plate) (Mortelmans 1986).
>
> In a separate study, negative results were reported when testing *S. typhimurium* strains TA1535 and TA1537 both with and without metabolic activation with induced rat liver S9 mix as well as strain TA1538 with metabolic activation. Unequivocal dose-response relationships were observed with strains TA98 and TA100 with and without metabolic activation and in strain TA1538 with metabolic activation. The concentrations used in these experiments ranged from 0.1-10.0 µg/plate while toxicity was reported at levels of 10-50 µg/plate (Gelernt and Herbert. 1982).
>
> Diisopropylamine was negative when tested in the DNA repair assay in cultured rat hepatocytes at concentrations of 0.1-5000 µg/mL (preliminary assay) and 10-2500 µg/mL (replicate assay). The compound was cytotoxic at a concentration of 5000 µg/mL. At concentrations of 500 µg/mL and above, pH changes of the test media occurred, which was not adjusted for (Long 1986).

> The committee did not find other data on in vitro and in vivo mutagenicity/genotoxicity tests."

4.2.2 In Vivo Tests

TCEQ did not find any data on *in vivo* mutagenicity/genotoxicity tests. Two-year chronic inhalation carcinogenic studies have not been conducted.

4.2.3 Carcinogenicity

There is no evidence that DIPA is carcinogenic. Based on the Guidelines for Carcinogen Risk Assessment (USEPA 2005), the most appropriate cancer classification descriptor for DIPA would be inadequate information to assess carcinogenic potential via the inhalation pathway.

4.3 Welfare-Based Chronic ESL

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

4.4. Long-Term ESL

The chronic evaluation using a weight of evidence approach to determine the most defensible chronic toxicity factors derived from three different approaches indicates that the category/read across approach is the preferred method to set the generic chronic ESL.

The $^{chronic}ESL_{generic}$ based on a RPF approach is likely biased low (Section 4.1.9.2). There is uncertainty in using a 30-d rodent study (the cutoff between a subacute and subchronic study) to develop a chronic ReV. In addition, the derived chronic ReV and $^{chronic}ESL_{threshold(nc)}$ are likely biased low because a cumulative UF of 2,700 from five different UF categories was used to adjust the POD_{HEC} (Section 4.1.7). Accordingly, a chronic ReV was not developed based on the 30-d study, and a category/read across approach was used to determine a chronic ReV and ESL based on DBA's $^{chronic}ESL_{threshold(nc)}$ (Section 4.1.9.1).

- Chronic ReV = 18 µg/m^3 (4.3 ppb)
- ^{chronic}ESL = 5.4 µg/m^3 (1.3 ppb)

The long-term ESL for DIPA used for air permit evaluations is 5.4 µg/m^3 (1.3 ppb) (Table 2).

4.5 Subchronic Inhalation Observed Adverse Effect Levels

The critical endpoint used in the subchronic evaluation, (corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates), was also used as the basis for calculation of a chronic inhalation observed adverse effect level applicable for a one-month exposure. The LOAEL of 100 mg/m^3 determined using data from Roloff and Ruecker (1987) was used as the POD. No duration adjustment was made (TCEQ 2015a). However, an animal-to-human dosimetric adjustment was made to calculate a POD_{HEC} of 100 mg/m^3.

The subchronic inhalation observed adverse effect level 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 (i.e., one month). Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The subchronic inhalation observed adverse effect level of 100 mg/m^3 (24 ppm) is provided for informational purposes only (TCEQ 2015a). 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.

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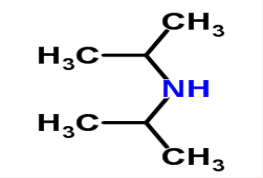
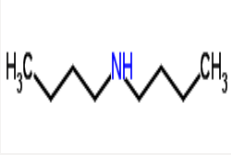
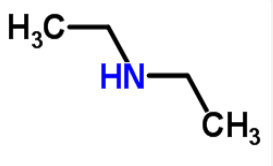
Appendix A Consideration of a Category/Read-Across Approach

A.1 Comparison of Physical/Chemical Properties

DIPA, DBA and diethylamine (DEA) are secondary amines. They are structurally similar, have similar physical/chemical properties (Table 10), and are expected to have similar MOAs.

Table 10 Comparison of Physical/Chemical Properties for DIPA, DBA and DEA

Parameter	**DIPA**	**DBA**	**DEA**
Molecular Formula	$C_6H_{15}N$	C8-H19N	$C_4H_{11}N$
Chemical Structure			
Molecular Weight ($gmol^{-1}$)	101.191	129.24	73.1
Physical State at 25°C	Liquid	Liquid	Liquid
Color	Colorless	Colorless	Colorless
Odor	Ammonia, fish-like odor	Ammonia-like odor	Ammonia, fish-like odor
CAS Number	108-18-9	111-92-2	109-89-7
Solubility in water	110 g/L at 25°C	3.5 g/L at 25 °C	Miscible
Log Kow	1.4	2.83	0.58
pKa	11.07	11.31	11.09
Density (water = 1)	0.7169	0.7601 at 20 °C	0.71
Vapor Pressure	79.4 mm Hg at 25 °C	2.59 mm Hg at 25 °C	192 mm Hg
Melting Point	-61 °C	-60 to -59 °C	-50 °C
Boiling Point	84°C	159-160 °C	132°F

A.2 Read-Across Approach

OECD (2013) reports a SIDS Initial Assessment Profile that provides a summary of toxicity data read across approach for the aliphatic secondary amine category. The report states that aliphatic secondary amines have similar physical/chemical properties, structure-activity and are expected to have similar metabolism and MOAs. OECD (2013) used a read-across approach for addressing the mammalian and environmental endpoints where no data were available on individual category members. Using the category approach, category members with limited toxicity data are considered the same as the worst case read across approach.

The TCEQ derived a chronic ReV of 18 µg/m^3 (3.4 ppb) and 33 µg/m^3 (11 ppb) and a $^{chronic}ESL_{threshold(nc)}$ of 5.4 and 9.9 µg/m^3 for DBA and DEA, respectively (TCEQ 2015c, 2015d). Table 12 provides a summary of toxicity data read-across approach for DIPA, DBA and DEA. Using the OECD read-across approach, the lowest chronic ReV of 18 µg/m^3 and an ESL 5.4 µg/m^3 for DBA were selected as the DIPA's chronic ReV and ESL (Table 11).

Table 11 Summary of Toxicity Data Read Across Approach for DIPA, DBA and DEA

Parameter	Values for DIPA	Values for DBA	Values for DEA
Inhalation Lethality (LC_{50})	2800 mg/m^3 (2-h), 5300 mg/m^3 (4-h)	2370 mg/m^3 (1-h), 1,150 mg/m^3 (4-h)	11960 mg/m^3 (4-h)
Acute Inhalation Toxicity	LOAEL = 62 ppm (mice, 3-d), 24 ppm (rats, one-month) NOAEL = NA	LOAEL = 85.5 ppm (rats, 3-d) NOAEL= 28.5 ppm (rats, 3-d)	LOAEL = 10 ppm (human 1-h), 31 ppm (mice, 17-d), 62.5 ppm (rats, 16-d) NOAEL = 31 ppm (rats, 16-d)
Chronic/Subchronic Inhalation Toxicity Color	LOAEL = 24 ppm [b] (rats, 1 month) NOAEL = NA	LOAEL = 85.5 ppm [b] (rats, 28-d) NOAEL = 28.5 ppm (rats, 28-d) LOAEL = 28.5 ppm [c] (rats, 91-d NOAEL = 9.5 ppm (rats, 91-d)	LOAEL = 16 ppm (mice, 2 yr), 31 ppm (rats, 2 yr) NOAEL = 25 ppm (rats, 24-wk)
Gene Mutation In Vitro	Negative	Negative	Negative
Chromosome Aberration In Vitro	Negative	Positive/Marginal	Not Available
Chromosome Aberration In Vivo	Not available	Negative	Negative
Chronic ReV	**18 µg/m^3 [a] (read-across)**	**18 µg/m^3 (3.4 ppb)**	**33 µg/m^3 (11 ppb)**
Long-Term ESL	**5.4 µg/m^3 [a] ^{chronic}ESL (read-across)**	**5.4 µg/m^3 (1.0 ppb) ^{chronic}ESL$_{threshold(nc)}$**	**9.9 µg/m^3 (3.3 ppb) ^{chronic}ESL$_{threshold(nc)}$**

[a] Surrogated to DBA's Chronic ReV and ^{chronic}ESL$_{threshold(nc)}$

[b] For a critical effect of hyperplasia and metaplasia in respiratory epithelium

[c] For a critical effect of decrease in body weight

Appendix B Consideration of a Relative Potency Approach Based on DBA

Since chemical-specific chronic toxicity data in humans or animals were not available for DIPA, the TCEQ investigated the use of a relative potency approach based on DBA. DBA was chosen as the index chemical because it has a subchronic study and a $^{chronic}ESL_{threshold(nc)}$ has been developed by the TCEQ (2015c). A $^{chronic}ESL_{generic}$ for DIPA was set based on a relative potency approach using DBA's $^{chronic}ESL_{threshold(nc)}$ (TCEQ 2015c).

One-month inhalation toxicity studies were available for both DIPA (Roloff and Ruecker 1987) and DBA (TCEQ 2015c). A NOAEL was not identified for DIPA. Therefore, the LOAEL for DIPA and DBA for a critical effect of hyperplasia and metaplasia in respiratory epithelium were used to derive a relative potency factor (RPF) (TCEQ 2015a). Table 12 provides the relevant information to calculate a RPF for DIPA based on DBA. After subchronic exposure, DIPA appears to more toxic than DBA.

A RPF was calculated as follows:

RPF = LOAEL for DIPA / LOAEL for DBA

RPF = (24 ppm) / (85.5 ppm)

RPF = 0.28

The $^{chronic}ESL_{generic}$ for DIPA was calculated by multiplying DBA's $^{chronic}ESL_{threshold(nc)}$ of 1.2 ppb by 0.28, which equals 0.34 ppb or 1.4 µg/m^3. There is uncertainty in the RPF because the exposure method for DIPA was whole-body and for DBA was nose only. The RPF is likely biased low.

Table 12 Calculation of the $^{chronic}ESL_{generic}$ for DIPA based on RPF

Parameter	DIPA	DBA
Study	Roloff and Ruecker (1987)	Buschmann et al. (2003)
GLP	Yes	Yes
Study Population	SD rats; (15 males and 15 females per group)	Crl: (W1) WU BR rats (10 males and 10 females per group)
Study Quality	Medium	Medium
Exposure Methods	Whole body exposures via inhalation to analytical concentrations of DIPA	Nose-only exposures via inhalation to analytical concentrations of DBA vapor
Exposure Concentrations	0 (control), 100, 600, or 2000 mg/m^3	0 (clean air), 50, 150, or 450 mg/m^3
Exposure Duration	6 h/day, 5 days/week for one month	6 h/day; 5 days/week for 28 days
Critical effects at one month	Corneal lesions, reduced leukocyte counts, and hyperplasia and metaplasia of the nasal turbinates	Decreased in body weight. Mucosal inflammatory cell infiltration and squamous metaplasia of the respiratory epithelium
LOAEL [a]	24 ppm (100 mg/m^3) [b]	85.5 ppm (450 mg/m^3) [b]
NOAEL	Not available	9.5 ppm (50 mg/m^3)
Relative Potency Factor [b]	24 ppm / 85.5 ppm = 0.28	- - -
Long-Term ESL	**1.4 µg/m^3 [c]** $^{chronic}ESL_{generic}$	**5.4 µg/m^3 (1.0 ppb)** $^{chronic}ESL_{threshold(nc)}$

[a] No duration or animal-to human dosimetric adjustments were made to the LOAEL

[b] Based on a critical effect of hyperplasia and metaplasia of the respiratory