Development Support Document
Final, July 8, 2016

Dibutylamine

CAS Registry Number: 111-92-2

Prepared by

Roberta L. Grant, Ph.D.

Jong-Song Lee, Ph.D.

Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Dibutylamine
Page i

Table of Contents

List of Tables

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
DBA	dibutylamine
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
F	female
GSD	geometric standard deviation (σ_g)

Acronyms and Abbreviations	Definition
h	hour(s)
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
M	male
MW	molecular weight
µg	microgram
µg/m^3	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute(s)
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

Acronyms and Abbreviations	Definition
OSHA	Occupational Safety and Health Administration
pKa	Acid dissociation constant
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 acute and chronic evaluations of dibutylamine (DBA). 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 DBA's physical/chemical data.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV [1 h]	910 µg/m^3 (170 ppb) **Short-Term Health**	**Critical Effect**: Adverse histopathology in the nasal region of rats
$^{acute}ESL_{odor}$	420 µg/m^3 (80 ppb) **Odor**	Fishy, ammonia-like odor
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	18 µg/m^3 (3.4 ppb) **Long-Term Health**	**Critical Effect(s)**: Decrease in body weight in male rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Inadequate information to assess carcinogenic potential via the inhalation pathway
$^{chronic}ESL_{veg}$	- - -	No data found

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

Dibutylamine
Page 2
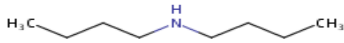
Table 2 Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
^{acute}ESL [1 h] (HQ = 0.3)	270 µg/m^3 (51 ppb)^a **Short-Term ESL for Air Permit Reviews**	**Critical Effect**: Adverse histopathology in the nasal region of rats
^{acute}ESL$_{odor}$	**420 µg/m^3 (80 ppb)**	Fishy, ammonia-like odor
^{acute}ESL$_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	5.4 µg/m^3 (1.0 ppb)^b **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s)**: Decrease in body weight in male rats
^{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 910 µg/m^3 (170 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.
^{b} Based on the chronic ReV of 18 µg/m^3 (3.4 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	C8-H19-N	ChemIDplus [a]
Chemical Structure		ChemIDplus [a]
Molecular Weight (gmol^{-1})	129.24	HSDB (1999) [a]
Physical State at 25°C	Liquid	HSDB (1999) [a]
Color	Colorless	HSDB (1999) [a]
Odor	Fishy, ammonia-like odor	HSDB (1999) [a]
CAS Registry Number	111-92-2	HSDB (1999) [a]
Synonyms	1-Butanamine, N-butyl- N-Butyl-1-butanamine n-Dibutylamine	ChemIDplus [a]
Solubility in water	3500 mg/L at 25 ºC	HSDB (1999) [a]
Log Kow	2.83	HSDB (1999) [a]
pKa	11.31	HSDB (1999) [a]
Density (water = 1)	0.7601 at 20 ºC	HSDB (1999) [a]
Vapor Pressure	2.59 mm Hg at 25 ºC	HSDB (1999) [a]
Melting Point	-60 to -59 °C	HSDB (1999) [a]
Boiling Point	159-160 °C	HSDB (1999) [a]
Conversion Factors	1 ppm = 5.29 mg/m^3 1 mg/m^3 = 0.19 ppm	TCEQ staff

[a] Accessed on August 18, 2015.

Chapter 2 Major Sources and Uses

HSDB (1999) provides the following information on DBA. In industry, DBA is used in cleaners, in cement, and as chemical precursors. In consumer products, DBA is used in drain openers, household cleaners for both ovens and bathrooms, hair relaxers, dishwasher soap, and in automobile air bags. DBA was found in the expired air of 6.5% of a sample of 54 normal, healthy, nonsmoking adults who resided in urban areas at a geometric mean concentration of 0.218 ng/L (Krotoszynski et al. 1979).

According to OECD (2013), the production volume for the United States for 2006 was between 4,536 and 22,680 tons. DBA 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.

Chapter 3 Acute Evaluation

OECD (2013) grouped DBA in their aliphatic secondary amine group in their SIDS Initial Assessment Profile. The OECD document provides a summary review of the toxicity of DBA. The TCEQ reviewed the toxicity information in the OECD document, and also conducted a thorough review of the literature.

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

According to NIOSH (2014), inhalation exposure to DBA can cause the following symptoms: sore throat, cough, burning sensation and shortness of breath. Labored breathing may also occur. Effects such as lung edema may be delayed - effects may be observed after a few hours of exposure and are made worse when accompanied with physical activity.

3.1.1 Physical/Chemical Properties

DBA is a colorless, flammable liquid at room temperature with a fishy, ammonia-like odor. It has a molecular weight of 129.24 g/mol and a vapor pressure of 2.59 mm Hg at 25ºC. DBA is soluble in water as well as in alcohol, ether, ethanol, and acetone (HSDB 1999). It has a log K_{ow} of 2.83 (HSDB 1999), which indicates it may be absorbed well through the skin (TCEQ 2015a). Other physical/chemical properties of DBA can be found in Table 3.

3.1.2 Key and Supporting Studies

There are no occupational or epidemiology studies in humans with adequate exposure data. Therefore, an animal study was used to derive the acute reference value (ReV).

3.1.2.1 Key Animal Study (Buschmann et al. 2003)

3.1.2.1.1 Study Details

Wistar rats [Crl:(WI)WU BR] were exposed nose-only to 99% pure DBA for 6 h/day(d) for 3 d. Toxicity was also assessed after exposures for 28 d and 91 d in order to evaluate effects after subacute and subchronic exposure, respectively. The 91-d study is discussed in Chapter 4.

The study was conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP). Five males and 5 females per group were exposed to 0 (clean air), 150, or 450 mg/m^3 DBA for the 3-d study and to 0 (clean air), 50, 150, or 450 mg/m^3 for the 28-d study (9.5, 28.5, 85.5 ppm). Analytical concentrations (mean ± S.D.) were verified by flame ionization detector and were 50.6 ± 5.5, 142.7 ± 9.7 and 448.2 ± 16 mg/m^3 DBA.

Rats were observed once daily for clinical symptoms, and body weight and food consumption were determined weekly. Gross pathology was performed and lungs were weighted. Histological examinations were done on the tissues of the respiratory tract (nasal cavity, larynx, laryngo-pharynx, trachea, lungs, and lung-associated lymph nodes).

Bronchoalveolar lavage (BAL) was performed on the left lung lobe. Leukocytes were determined as well as differential cell count for percent of macrophages, granulocytes, and lymphocytes.

3.1.2.1.2 Results

No clinical signs of toxicity were observed, except for animals exposed to 450 mg/m^3, slight convulsions were observed after exposure in the first days of exposure. According to Buschmann et al. (2003), this might be due to defensive reactions of the rats to exposure. There were no statistical differences in terminal body weights and absolute and relative lung weights after 3 d of exposure. Treatment-related gross pathology findings were not observed. BAL fluid analysis was not statistically different from controls. In the histopathological examination, significant irritating effects (e.g., ulceration, epithelial erosion, mucosal inflammatory cell infiltration, squamous metaplasia of the respiratory epithelium) in the nasal cavities were observed only in animals at 450 mg/m^3 after 3 d of exposure. Slight but not statistically significant histopathological effects in the lung were also observed.

After 28 d of exposure, treatment-related gross pathology findings were not observed. BAL fluid analysis was not statistically different from controls. Ulceration, epithelial erosion, and submucosal hemorrhage were not observed, possibly due to increased production of mucus (Buschmann et al. 2003). However, after subacute exposure, slight mucosal inflammatory cell infiltration, squamous metaplasia of the respiratory epithelium, and mucus (goblet) cell hyperplasia. There was a statistically significant decrease in terminal body weight (approximately a 10% decrease) observed in males at 450 mg/m^3 and a statistically significant increase in relative lung weight in females at 450 mg/m^3.

Histopathological findings in the nasal cavities after 3 and 28 d of exposure are shown in Table 4.

Table 4 Major Histopathological Findings in the Nasal Cavities after 3- and 28-Day Exposure

Lesions [a]	0 mg/m³ Clean Air	150 mg/m³	450 mg/m³	0 mg/m³ Clean Air	50 mg/m³	150 mg/m³	450 mg/m³
n/exposure	5M 5F 3-d	5M 5F 3-d	5M 5F 3-d	5M 5F 28-d	5M 5F 28-d	5M 5F 28-d	5M 5F 28-d
Ulceration	0/10	0/10	5/10 b	0/10	0/10	0/10	0/10
Epithelial erosion(s)	0/10	0/10	9/10 b	0/10	0/10	0/10	0/10
Mucosal inflammatory cell infiltration	0/10	0/10	10/10 b	0/10	0/10	0/10	6/10
Squamous metaplasia of the respiratory epithelium	0/10	0/10	10/10 b	0/10	0/10	0/10	5/10
Mucus (goblet) cell hyperplasia c	1/10	1/10	8/10 c	1/10	2/10	1/10	10/10
Submucosal hemorrhage	0/10	0/10	9/10 b	0/10	0/10	0/10	0/10
Mucosal/submucosal edema	0/10	0/10	1/10	0/10	0/10	0/10	0/10
Respiratory epithelial hyperplasia	0/10	0/10	0/10	0/10	0/10	0/10	0/10

[a] There were no substantial sex differences so data for males and females were combined.
[b] Adverse effects
[c] Considered an adaptive response.

3.1.2.1.3 Conclusions

The no-observed-adverse-effect level (NOAEL) after the 3- and 28-d exposure is 150 mg/m³ and the lowest-observed-adverse-effect level (LOAEL) is 450 mg/m³ for irritating effects in the nasal cavities. The levels of 150 and 450 mg/m³ are also a NOAEL and LOAEL, respectively, for terminal body weight and relative lung weight after the 28-d exposure.

3.1.2.2 Supporting Studies

3.1.2.2.1 Lethality Studies

A 1-hour (h) LC_{50} value of equal to or greater than 573 ppm was reported in 5 male and 5 female Sprague-Dawley (SD) rats (Pennwalt Corp 2000). Clinical observations included partial closing of eyes, reduced respiratory rate, exaggerated respiratory movements, hunched body posture and ataxia. Gross necropsy revealed no abnormalities.

A 4-h LC_{50} value of 1,150 mg/m^3 (220 ppm) (standard error of 95 mg/m^3) was reported in 5 male and 5 female SD albino rats (Huntingdon Research Centre 2000). Measure exposure concentrations were 760, 1,080, 1,180, 1,390, or 3,910 mg/m^3 of air for 4 h (144, 200, 224, 260, or 740 ppm). Clinical observations included excessive salivation, lacrimation, gasping, convulsions, abnormal breathing, ataxia, lethargy, rales, and staining of the urogenital area. Lung congestion in decedents was observed after gross necropsy was performed.

Greim et al. (1998) reported a 4-h LC_{50} value of 2,680 mg/m^3 (510 ppm). No details on species or the study was reported.

3.1.2.2.2 Respiratory Depression Studies

Male OF1 mice experienced expiratory bradypnea indicative of upper airway irritation after acute inhalation exposure. The calculated concentration resulting in a 50% decrease in respiratory rate (RD_{50}) in mice was 173 ppm (Gagnaire et al. 1993). In tracheal-cannulated mice, an RD_{50} of 106 ppm (indicative of pulmonary sensory irritation) was reported (Gagnaire et al. 1993).

Nielsen and Yamagiwa (1989), using male Ssc:CF-1 mice, reported an RD_{50} of 81 ppm (indicative of upper respiratory sensory irritation). In tracheal-cannulated mice, an RD_{50} of 101 ppm (indicative of pulmonary sensory irritation) was reported.

3.1.2.3 Reproductive/Developmental Studies

Short-term reproductive/developmental studies have not been conducted for DBA. The alkyl amine class of compounds has generally not been shown to have reproductive/developmental effects except at doses/concentrations where maternal toxicity to treated animals occurs (OECD 2011, 2013).

3.1.2.4 Sensitization Potential

There is no clear evidence of skin sensitization potential for DBA (CEBS 2015; OECD 2013). Refer to Appendix A for additional details.

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

DBA is strongly alkaline, with an acid dissociation constant (pKa) of 11.31 (HSDB 1999). It has a log K_{ow} of 2.83 (HSDB 1999), which indicates it will be absorbed well and may bioconcentrate. 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.

DBA is assumed to have a threshold MOA which is relevant to humans. The exposure concentration of the chemical was used as the dose metric.

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

DBA causes the following abnormal histopathology in the nasal region of rats at a 3-d exposure to 450 mg/m^3: ulceration, epithelial erosion, mucosal inflammatory cell infiltration, squamous metaplasia of the respiratory epithelium, and submucosal hemorrhage. Mucus (goblet) cell hyperplasia also was observed, but this was considered an adaptive response. The NOAEL is 150 mg/m^3, which will conservatively be used as the POD for derivation of the acute (1-h) ReV.

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

The effects of DBA are assumed to be concentration- and duration-dependent. The POD of a single day 6-h exposure duration (C_1) was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge (1986) (C_1^n x $T_1 = C_2^n$ x T_2) with n = 3, where both concentration and duration play a role in toxicity:

$$POD_{ADJ} = C_2 = [(C_1)^3 \text{ x } (T_1 / T_2)]^{1/3}$$
$$POD_{ADJ} = [(150 \text{ mg/m}^3)^3 \text{ x } (6 \text{ h/1 h})]^{1/3}$$
$$= 272.6 \text{ mg/m}^3$$

3.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

The health effects produced by DBA 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 in order to calculate a POD_{HEC} (TCEQ 2015a). A default value of 1 was used for the Regional Gas Dose Ratio (RGDR) for a Category 1 vapor with ET respiratory effects (TCEQ 2015a).

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

$$POD_{HEC} = POD_{ADJ} \text{ x } RGDR_{ET}$$
$$= 272.6 \text{ mg/m}^3 \text{ x } 1$$
$$= 272.6 \text{ mg/m}^3$$

3.1.6 Adjustment of the POD$_{HEC}$ and Application of Uncertainty Factors

The POD$_{HEC}$ of 272.6 mg/m^3 was based on abnormal histopathology in the nasal region of the rat (Buschmann et al. 2003), which is assumed to have a threshold MOA. The default for threshold effects is to determine a POD and apply uncertainty factors (UFs) to derive a ReV. The

following UFs were applied to the POD_{HEC}: 10 for intraspecies variability (UF_H), 3 for animal-to-human uncertainty (UF_A), and 10 for the database completeness (UF_D), for a total UF = 300.

- a UF_H of 10 was used to account for potential variation in sensitivity among the members of the human population (e.g., possible child/adult differences, those with pre-existing medical conditions). .

- a UF_A of 3 was used because dosimetric adjustment from animal-to-human exposure was conducted, which accounts for toxicokinetic differences but not toxicodynamic differences.

- a UF_D of 10 was used because only one acute study in one species (rats) was available which used only 5 males and 5 females per group (Buschmann et al. 2003). Short-term reproductive/developmental studies are not available for DBA, although, in general, the amine class has not been shown to cause reproductive/developmental effects. Information on potential sensory irritation in humans for DBA is not available. For diethylamine (TCEQ 2015c), human sensory eye irritation occurred in humans (Lundqvist et al. 1992) at lower concentrations than histopathology effects in rats and mice (NTP 2011). Nielsen and Yamagiwa (1989) determined an RD_{50} for diethylamine of 184 ppm and an RD_{50} for DBA of 81 ppm, indicating DBA may be as potent or a more potent sensory irritant than diethylamine.

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

$$= 272.6 \text{ mg/m}^3/(10 \text{ x } 3 \text{ x } 10)$$
$$= 272.6 \text{ mg/m}^3/300$$
$$= 0.9087 \text{mg/m}^3$$
$$= 908.7 \text{ µg/m}^3 \text{ or } 910 \text{ µg/m}^3 \text{ (rounded to two-significant figures)}$$

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 910 µg/m^3 (170 ppb). 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 270 µg/m^3 (51 ppb) (Table 7). Table 7 provides a summary of the toxicity assessment for DBA. The quality of the Buschmann et al. (2003) study is medium and the confidence in acute database is low.

Table 5 Derivation of the Acute ReV and acuteESL

Parameter	Summary
Study	Buschmann et al. (2003)
Study Population	5 male and 5 female rats per exposure group
Study Quality	Medium
Exposure Methods	Nose-only exposures via inhalation to analytical concentrations of DBA vapor
Exposure Concentrations	0 (clean air), 150, and 450 mg/m^3
Exposure Duration	6 h/d for 3 d
Critical Effect(s)	Adverse histopathology in the nasal region
LOAEL	450 mg/m^3
NOAEL	150 mg/m^3
POD$_{ADJ}$ (1 h)	272.6 mg/m^3
POD$_{HEC}$	272.6 mg/m^3
Total Uncertainty Factors (UFs)	300
Interspecies UF	10
Intraspecies UF	3
Incomplete Database UF	10
Database Completeness	Low
acute ReV [1 h] (HQ = 1)	**910 µg/m^3 (170 ppb)**
acuteESL [1 h] (HQ = 0.3)	**270 µg/m^3 (51 ppb)**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

DBA has a fishy, ammonia-like odor (HSDB 1999). Hellman and Small (1974) reported an odor detection, 50% odor recognition, and 100% odor recognition levels at 80, 270 and 480 ppb for DBA, respectively. The acuteESL$_{odor}$ for DBA, based on an evidence-integration approach (TCEQ 2015b) is 420 µg/m^3 (80 ppb).

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 = 910 µg/m^3 (170 ppb)
- ^{acute}ESL = 270 µg/m^3 (51 ppb)
- ^{acute}ESL$_{odor}$ = 420 µg/m^3 (80 ppb)

The short-term ESL for air permit evaluations is the health-based ^{acute}ESL of 270 µg/m^3 (51 ppb) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

The 3-d LOAEL value of 450 mg/m^3 determined in rats from Buschmann et al. (2003) was adjusted to a human equivalent concentration (LOAEL$_{HEC}$) of 450 mg/m^3. No duration adjustment was made (TCEQ 2015a). Therefore, 450 mg/m^3 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.

The LOAEL$_{HEC}$ determined from animal 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 (i.e., $\geq$ 450 mg/m^3 for 6 h/d for 3 d). 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.

The margin of exposure between the estimated 6-h/3-d subacute inhalation observed adverse effect level of 450 mg/m^3 and the 1-h acute ReV of 0.910 mg/m^3 (910 µg/m^3) is a factor of 495.

Chapter 4 Chronic Evaluation

OECD (2013) recently reviewed the toxicity of DBA, although it provides summary information only. The TCEQ reviewed the toxicity information in this document and also conducted a thorough review of the literature.

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties

DBA has a log K_{ow} of 2.83 (HSDB 1999), which indicates it may be absorbed well through the skin and has potential to bioconcentrate. For other physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.2 Key Study (Buschmann et al. 2003)

There are no published epidemiology studies or reports of chronic health effects in humans with adequate DBA exposure data. Therefore, an animal study was used to derive the chronic ReV. Of the available animal studies, no chronic inhalation studies were identified and only one subchronic study was identified. The subchronic animal study was conducted by Buschmann et al. (2003) and was used to derive the chronic ReV.

4.1.2.1 Study Details

Wistar rats [Crl:(WI)WU BR] were exposed nose-only to 99% pure DBA for 6 h/d, 5 d/week for 91 ds. Refer to Section 3.1.2 for a description of the 3-d and 28-d studies conducted by Buschmann et al. (2003).

The 91-d study was conducted in compliance with the OECD Principles of GLP. Five males and 5 females were used in the 0 (clean air) control group. Ten males and 10 females per group were exposed to 50, 150, or 450 mg/m^3 (9.5, 28.5, or 85.5 ppm). Analytical concentrations (mean ± S.D.) were verified by flame ionization detector and were 50.6 ± 5.5, 142.7 ± 9.7 and 448.2 ± 16 mg/m^3 DBA.

Rats were observed once daily for clinical symptoms, and body weight and food consumption were determined weekly. Gross pathology was performed and lungs were weighed. Histological examinations were done on the tissues of the respiratory tract (nasal cavity, larynx, laryngo-pharynx, trachea, lungs, and lung-associated lymph nodes).

BAL was performed on the left lung lobe. Leukocytes were determined as well as differential cell count for percent of macrophages, granulocytes, and lymphocytes.

4.1.2.2 Results

There were no statistical differences in absolute and relative lung weights. Treatment-related gross pathology findings were not observed. BAL fluid analysis was not statistically different from controls. Histopathological findings in the nasal cavities after 91 d of exposure are shown in Table 6. There were no significant changes in histopathological findings except for a marked increase in respiratory epithelial hyperplasia at the highest concentration of 450 mg/m^3.

DBA produced statistically significant decreases in body weight in males at 150 and 450 mg/m^3 (ANOVA and Dunnett's tests (two-sided)):

- 0 (clean air) control group: 366.3 + 21.6 g (mean, standard deviation):
- 50 mg/m^3: 356.7 + 19.9 g
- 150 mg/m^3: 325.1 + 25.2 g (p < 0.05)
- 450 mg/m^3: 313.0 + 36.1 g (p < 0.01)

4.1.2.3 Conclusions

For decreases in terminal body weight, the NOAEL is 50 mg/m^3 and the LOAEL is 150 mg/m^3. For marked increase in respiratory epithelial hyperplasia, the NOAEL is 150 mg/m^3 and the LOAEL is 450 mg/m^3. Mucus (goblet) cell hyperplasia also was observed in treated animals, but this was considered an adaptive response. Other histopathological lesions observed after a 3-d exposure (ulceration, epithelial erosion, and submucosal hemorrhage) (Table 4) were not observed after a 91-d exposure. Buschmann et al. (2003) indicated that this might be due to the increased production of mucus due to mucus and DBA might not reach epithelial cells after 28 or 91 d of exposure, or might reach them only in diluted form. There might not yet be enough mucus available after 3 d of exposure.

Table 6 Major Histopathological Findings in Nasal Cavities after 91 Days of Exposure

	0 Clean Air	50 mg/m^3	150 mg/m^3	450 mg/m^3
Lesions	**5 M 5 F**	**10 M 10 F**	**10 M 10 F**	**10 M 10 F**
Ulceration	**0/10 [a]**	**0/20**	**0/20**	**0/20**
Epithelial erosion(s)	**0/10**	**0/20**	**0/20**	**0/20**
Mucosal inflammatory cell infiltration	**0/10**	**0/20**	**0/20**	**0/20**
Squamous metaplasia of the respiratory epithelium	**0/10**	**0/20**	**0/20**	**0/20**
Mucus (goblet) cell hyperplasia [b]	**1/10**	**4/20**	**15/20**	**20/20**
Submucosal hemorrhage	**0/10**	**0/20**	**0/20**	**1/20**
Mucosal/submucosal edema	**0/10**	**2/20**	**0/20**	**3/20**
Respiratory epithelial hyperplasia	**0/10**	**0/20**	**0/20**	**10/20**

[a] There were no substantial sex differences so data for males and females were combined.
[b] Considered an adaptive response.

4.1.3 MOA Analysis and Dose Metric

The MOA for DBA after chronic exposure is similar to the MOA after acute exposure. DBA is strongly alkaline, with an acid dissociation constant (pKa) of 11.31 (HSDB 1999). 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.

Adverse effects occur mainly in the upper respiratory tract, although after chronic exposure, systemic effects such as decrease in body weight in male rats were observed at lower concentrations than upper respiratory tract effects. The MOA for systemic effects is unknown. Adverse effects produced by DBA is assumed to have a threshold MOA and are relevant to humans. The exposure concentration of the chemical was used as the dose metric.

4.1.4 Benchmark Dose Modeling

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.6.0.1) (available at http://www.epa.gov/ncea/bmds/) for decrease in terminal body weights in male rats. Data for increase in respiratory epithelial hyperplasia were not amenable to BMC modeling since adverse effects only occurred at the highest concentration. The LOAEL for decreases in terminal body weight is 150 mg/m^3 and the NOAEL is 50 mg/m^3.

Decrease in terminal body weights in male rats was modeled using continuous models. A default BMR of 10% decrease in body weight was used (TCEQ 2015a). The results for 1 standard deviation (SD) as a benchmark response level were also provided (USEPA 2012). The 95% lower confidence limits on the BMC_{10} and $BMC_{1\,SD}$ were calculated, as shown in Table 7, which shows a summary of pertinent BMC modeling data. Please refer to Appendix B for detailed information. The BMC_{10} was 122 mg/m^3 and the $BMCL_{10}$ was 54.9 mg/m^3.

Table 7 BMC Results for the Best Fit Model for the Examined Endpoints

Endpoint	Best Model	p value	AIC	Scaled Residual	mg/m^3	mg/m^3
Decrease in body weight [a]	Exponential (M4)	0.357	270.73	$< \lvert 2 \rvert$	BMC_{10} 122	$BMCL_{10}$ 54.9 [a]
Hyperplasia of rat respiratory epithelium,	No acceptable models	---	---	---	LOAEL 450	NOAEL 150

[a] Chosen as the critical effect.

4.1.5 Critical Effect and POD

The LOAELs/NOAELs based on respiratory effects are higher than the $BMC_{10}/BMCL_{10}$ for decrease in body weight (Table 7). The POD for decrease in terminal body weight in male rats, the critical effect, is the $BMCL_{10}$ of 54.9 mg/m^3. If systemic effects are prevented, then respiratory effects will be prevented.

4.1.6 Dosimetric Adjustments

4.1.5.1 Default Exposure Duration Adjustments

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

$$POD_{ADJ} = POD \times (D/24\ h) \times (F/7\ d)$$

where: D = Exposure duration, hours per day
F = Exposure frequency, days per week

$$POD_{ADJ} = 54.9\ mg/m^3 \times (6/24) \times (5/7) = 9.8036\ mg/m^3$$

4.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

DBA is water soluble as well as lipid soluble. It produces remote effects at lower concentrations than respiratory effects. Animal-to-human dosimetric adjustments will be conducted as a Category 3 gas. For category 3 gases:

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

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

Chemical-specific data on $((H_{b/g})_A$ or $(H_{b/g})_H)$ for DBA are not available, so a default value of 1 is used for the regional gas dose ratio (RGDR) (TCEQ 2015a).

$$POD_{HEC} = POD_{ADJ} \times ((H_{b/g})_A / (H_{b/g})_H) = 9.8036\ mg/m^3 \times 1 = 9.8036\ mg/m^3$$

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

The lowest POD_{HEC} of 9.8036 mg/m^3 from the Buschmann et al. (2003) subchronic study was based on decreased body weight in male rats. 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 540:

- a UF_H of 10 was used to account for potential variation in sensitivity among members of the human population (e.g., possible child/adult differences, those with pre-existing medical conditions).
- 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_{Sub} of 3 was used to account for the uncertainty of using a subchronic study to predict toxicity after chronic exposure. A decrease in body weight occurred at 150 mg/m^3 after a 28-d exposure and at 50 mg/m^3 after a 91-d exposure (a three-fold difference). A UF_{Sub} of 1 was not used because the log K_{ow} of DBA indicates that bioaccumulation may occur and data indicate that longer exposure produces decreased body weight at a somewhat lower concentration.
- a UF_D of 6 was used because only one subchronic study in one species was available. The critical effect was decrease in body weight in male rats, based on 10 male rats (Buschmann et al. 2003). Short-term reproductive/developmental studies are not available for DBA, although in general, the amine class has not been shown to cause reproductive/developmental effects. The study quality is medium. Database completeness is considered medium to low.

$$\text{Chronic ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_{Sub} \; UF_D)$$
$$= 9.8036 \text{ mg/m}^3 / (10 \times 3 \times 1 \times 3 \times 6)$$
$$= 9.8036 \text{ mg/m}^3 / 540$$
$$= 0.0181 \text{ mg/m}^3$$
$$= 18 \text{ µg/m}^3 \text{ (rounded to two significant digits)}$$

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 18 µg/m^3 (3.4 ppb). 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 5.4 µg/m^3 (1.0 ppb) (Table 9). Study quality was medium, but database completeness is medium to low.

Table 8 Derivation of the Chronic ReV and $^{\text{chronic}}$**ESL**$_{\text{threshold(nc)}}$

Parameter	Summary
Study	Buschmann et al. (2003)
Study Population	Crl: (W1)WU BR female and male rats (10 males and 10 females per group exposed to DBA)
Study Quality	Medium
Exposure Method	Nose-only exposures via inhalation to analytical concentrations of DBA vapor
Exposure Concentrations	0 (clean air), 50, 150, and 450 mg/m^3
Exposure Duration	6 h/d, 5 d/week for 91 d
Critical Effects	Decrease in body weight in male rats
POD for observed adverse effect level (BMC$_{10}$)	122 mg/m^3
POD (BMCL$_{10}$)	54.9 mg/m^3
Extrapolation to continuous exposure (POD$_{\text{ADJ}}$)	9.8036 mg/m^3
POD$_{\text{HEC}}$	9.8036 mg/m^3
Total UFs	540
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	Not available
Subchronic UF	3
Incomplete Database UF Database Completeness	6 Low
Chronic ReV (HQ = 1)	**18 μg/m^3 (3.4 ppb)**
$^{\text{chronic}}$**ESL**$_{\text{threshold(nc)}}$ **(HQ = 0.3)**	**5.4 μg/m^3 (1.0 ppb)**

4.2 Carcinogenic Potential

4.2.1 In Vitro Assays

Ishidate and Odashima (1977) tested DBA (in 1% ethanol) at a concentration of 4 mg/ml (1×10^{-4} molar) in Chinese hamster cells. The observed effects were chromatid gaps, chromatid or chromosomal breaks and translocation in 6% of Chinese hamster cells. Tanooka (1977) used a mutagen-tester of Bacillus subtilis, which was almost equivalent with a somewhat broader detection spectrum than the Salmonella typhimurium TA100 system. In a growth inhibition test using this strain, there was a positive indication of excision and amplification or recombination of repair-dependent DNA damage produced by DBA.

Using a standard protocol for the Salmonella/microsome preincubation assay (approved by the National Toxicology Program), DBA was tested for mutagenicity at doses of 0.10, 0.33, 1.0, 3.3, and 10 mg/plate in TA1535, TA1537, TA97, TA98, and TA100 Salmonella typhimurium strains. Tests were conducted in the presence and absence of rat or hamster liver S-9. DBA was negative in these tests (Mortelmans et al. 1986).

4.2.2 In Vivo Assay

Elf Atochem North America, Inc. (1995) investigated the clastogenic potential of DBA in Harlan SD ICR mice (20/sex/group) via oral gavage at doses of 55, 110, or 220 mg/kg body weight. At 24, 48 or 72-hour post-treatment, there was no significant increase in micronucleated polychromatic erythrocytes at the post-treatment examination in either male or female treated mice compared to controls.

4.2.3 Cancer Classification

The results for DBA in the above in vitro and in vivo tests are conflicting. Two-year inhalation carcinogenicity studies on DBA are not available. However, structural analogues of DBA such as diethylamine have shown no evidence of carcinogenicity after a 2-year National Toxicology Program study (NTP 2011; TCEQ 2015c). Based on the Guidelines for Carcinogen Risk Assessment (USEPA 2005), the most appropriate cancer classification descriptor for DBA 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 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 = 18 $\mu g/m^3$ (3.4 ppb)

- $^{chronic}ESL_{threshold(nc)}$ = 5.4 µg/m^3 (1.0 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 5.4 µg/m^3 (1.0 ppb) (Table 2).

4.5 Subchronic Observed Adverse Effect Level

The critical endpoint used in the chronic evaluation, decrease in body weight in male rats, was also used as the basis for calculation of a subchronic inhalation observed adverse effect level. The BMC$_{10}$ value of 122 mg/m^3 determined using data from Buschmann et al. (2003) 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 122 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., $\geq$ 6 h/d, 5 d/week for 91 d). Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The subchronic inhalation observed adverse effect level of 120 mg/m^3 (22 ppm) (rounded to two significant figures) 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.

The margin of exposure between the estimated subchronic inhalation observed adverse effect level of 120 mg/m^3 and the chronic ReV of 0.018 mg/m^3 (18 µg/m^3) is a factor of over 6,600..

Chapter 5 References

Buschmann, J, C Dasenbrock, R Fuhst, G Pohlmann, W Bartsch, O Creutzenberg, H Ernst, M Ketkar, B Schneider, H Ott. 2003. Effects of di-n-butylamine on the respiratory system of Wistar (WU) rats after subchronic inhalation. Inhal Toxicol 15:701-13.

Chemical Effects in Biological Systems (CEBS). 2015. National Institute of Environmental Health Studies (NIEHS) Toxicity Effects, CAS Registry Number: 111-92-2 http://tools.niehs.nih.gov/cebs3/ntpviews/index.cfm?action=testarticle.toxicity&cas_number=111-92-2#Metabolism/Metabolites [accessed 9-1-2015].

Chem IDplus A Toxnet Database 2015. Dibutylamine 111-92-2. available at http://chem.sis.nlm.nih.gov/chemidplus/rn/111-92-2 [accessed 8-18-15].

Elf Atochem North America Inc. 1995. Final Report, Micronucleus Cytogenetic Assay in Mice, with Cover Letter Dated 10/26/95; 10/05/95; EPA Document No. 86960000057; Fiche No. OTS0558197 (as cited in CEBS 2015).

Gagnaire, F, S Azim, P Simon, B Cossec, P Bonnet, and J De Ceaurriz. 1993. Sensory and pulmonary irritation of aliphatic amines in mice: A structure-activity relationship study. J Applied Toxicology 13: 129-135

Greim, H, D Bury, H-J Klimisch, M Oeben-Negele, K Ziegler-Skylakakis. 1998. Toxicity of aliphatic amines: Structure-activity relationship. Chemosphere 36: 271–295.

Hazardous Substance Data Base (HSDB) 1999. Dibutylamine. [accessed on 8-18-2015].

HellmanTM and FH Small. 1974. Charaterization of the odor properties of 101 petrochemicals using sensory methods. J Air Poll Control Asso 24(10): 979-982.

Huntingdon Research Centre. 2000. Acute inhalation toxicity in rats using dibutylamine: Four hour exposure. EPA/OTS; Doc #86-870000540 (as cited in CEBS 2015).

Ishidate, M Jr, and S Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro--a screening for chemical carcinogens. Mutat Res. 48(3-4): 337-53. (as cited in CEBS 2015).

Krotoszynski, BK, GM Bruneau, and HJ O'Neill.1979. Measurement of chemical inhalation exposure in urban population in the presence of endogenour effluents. ; J Anal Toxicol 3: 225-34.

Lundqvist, GR, M Yamagiwa, OF Pedersen, GD Nielsen. 1992. Inhalation of diethylamine—acute nasal effects and subjective response. American Industrial Hygiene Association Journal 53(3): 181-185.

Mortelmans, K, S Haworth, T Lawlor, W Speck, B Tainer, E Zeiger. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen 8 Suppl 7:1-119.

National Institute of Occupational Safety and Health (NIOSH). 2014. International Chemical Safety Card Di-n-butylamine. Available at http://www.cdc.gov/niosh/ipcsneng/neng1337.html [accessed August 18, 2015].

National Toxicology Program (NTP). (2011). NTP technical report on the toxicology and carcinogenesis studies of diethylamine (Cas no. 109-89-7) in F344/n rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Institutes of Health. NTP TR 566, NIH Publication No. 12-908 http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr566.pdf [accessed June 24, 2014].

Nielsen, GD, and M Yamagiwa. 1989. Structure-activity relationships of airway irritating aliphatic amines. Receptor activation mechanisms and predicted industrial exposure limits. Chem.-Biol. Interactions 71: 223-244.

Organisation for Economic Co‑operation and Development (OECD). 2013. CoCAM4, 16-18 April 2013. US/ICCA. SIDS Initial Assessment Profile, Aliphatic Secondary Amines http://webnet.oecd.org/hpv/ui/handler.axd?id=D79CCEC2-4FF0-4DA5-88DE-9690EA9F3FF9 [accessed 4-28-2015].

Pennwalt Corp. 2000. Acute inhalation toxicity in rats using dibutylamine: One-hour exposure. Govt Reports Announcements & Index (GRA & I), Issue 22, 2008 (abstract only).

Tanooka, H. 1977 Development and applications of Bacillus subtilis test systems for mutagens, involving DNA-repair deficiency and suppressible auxotrophic mutations. Mutat Res. 42(1):19-31 (as cited in CEBS 2015).

ten Berge, W F, A Zwart and LM Appelman. 1986. Concentration—time mortality response relationship of irritant and systemically acting vapours and gases. Journal of Hazardous Materials 13(3): 301-309.

Texas Commission on Environmental Quality (TCEQ). 2015a. TCEQ guidelines to develop toxicity factors (Revised RG-442). Texas Commission on Environmental Quality. Office of the Executive Director. Austin, TX

Dibutylamine
Page 22

Texas Commission on Environmental Quality (TCEQ). 2015b. Approaches to derive odor-based values. Texas Commission on Environmental Quality. Office of the Executive Director, Austin, TX.

Texas Commission on Environmental Quality (TCEQ). 2015c. Development support document diethylamine, CAS registry numbers: 109-89-7 (Proposed)., Office of the Executive Director, Austin, TX

United States Environmental Protection Agency (USEPA). 2005. Guidelines for Carcinogen Risk Assessment. (EPA/630/P-03/001B). United States Environmental Protection Agency. Washington, D.C.

United States Environmental Protection Agency (USEPA). 2012. Benchmark Dose Technical Guidance Document. (EPA/100/R-12/001). Washington, D.C.

Appendix A Dermal Sensitization Potential (CEBS 2015)
Taken directly from CEBS (2015):

> The dermal sensitization potential of di-n-butylamine (CAS # 111-92-2) was evaluated in 10 CF1(BR) mice inducted with 3 daily 0.1 ml topical applications of a 0.1% (v/v in ethanol) test solution to clipped abdomens. A group of 10 mice likewise inducted over 3 d with 0.1 ml dermal applications of 0.5% (w/v) DNCB served as the positive control. Challenge and rechallenge were administered 7 and 14 d later in .01 ml dermal applications of a 25% (v/v) solution to both dorsal and ventral surfaces of the left and right ears respectively of inducted test mice. The thickness of treated left ears relative to that of solvent control (ethanol) right ears indicated the degree of sensitization. One animal challenged with di-n-butylamine exhibited a positive sensitization response (20% increase in ear thickness over control) at 48-hour evaluation only. None of either test or irritation control groups had responded to challenge by the 24-hour evaluation and none responded to rechallenge. Conversely, 60% and 50% positive response in the DCNB-inducted and challenged groups at 24-hour and 48-hour evaluations, respectively, confirmed the validity of the test system. **UNREVIEWED**

Reference
Virginia Chemicals; Mouse Ear Swelling Test (Sensitization Assay) of Di-n-Butylamine; 05/27/87; EPA Doc. No. 86-870000820; Fiche No. OTS0515258 (cited in Chemical Effects in Biological Systems (CEBS). 2015. Toxicity Effects CAS Registry Number: 111-92-2. National Institute of Environmental Health Sciences http://tools.niehs.nih.gov/cebs3/ntpviews/index.cfm?action=testarticle.toxicity&cas_number=111-92-2) [accessed 9-3-2015].

Appendix B BMC Summary of Body Weight Decrease

Table 9 Summary of BMD Modeling Results for decreased body weight in male rats; BMR = 10% rel. dev. from control mean

Model[a]	Goodness of fit		BMD$_{10RD}$	BMDL$_{10RD}$	Basis for model selection
	p-value	AIC			
Exponential (M2) Exponential (M3)[b]	0.104	272.42	323	226	Of the models that provided an adequate fit and a valid BMDL estimate, the Exponential (M4) model was selected based on the lowest AIC and lowest BMDL.
Exponential (M4)	**0.357**	**270.73**	**122**	**54.9**	
Exponential (M5)	N/A[c]	271.89	131	62.5	
Hill	N/A[c]	271.89	127	error[d]	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.0909	272.68	336	242	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.225), selected model in bold; scaled residuals for selected model for doses 0, 50, 150, and 450 were -0.4, 0.64, -0.5, 0.14, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] No available degrees of freedom to calculate a goodness of fit value.
[d] BMD or BMDL computation failed for this model.
[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

Dibutylamine
Page 25

Exponential 4 Model, with BMR of 0.1 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
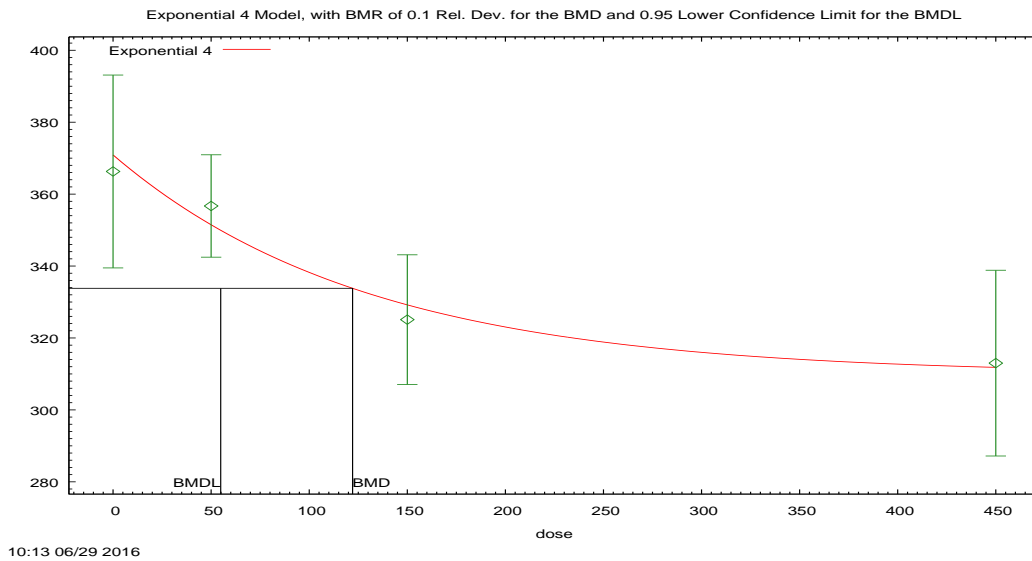
10:13 06/29 2016

Figure 1. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for decreased body weight; BMR = 10% rel. dev. from control mean; dose shown in mg/m³.

Exponential Model. (Version: 1.10; Date: 01/12/2015)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 10% Relative deviation

BMD = 122.111

BMDL at the 95% confidence level = 54.8918

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	6.50668	6.48243
rho	n/a	0
a	370.901	384.615
b	0.00766653	0.00433206
c	0.835492	0.775048
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	5	366.3	370.9	21.6	25.88	-0.3976
50	10	356.7	351.5	19.9	25.88	0.6388
150	10	325.1	329.2	25.2	25.88	-0.5017
450	10	313	311.8	36.1	25.88	0.144

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-130.9426	5	271.8852
A2	-128.7638	8	273.5275
A3	-130.9426	5	271.8852
R	-139.9246	2	283.8492
4	-131.367	4	270.7339

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	22.32	6	0.001059
Test 2	4.358	3	0.2253
Test 3	4.358	3	0.2253
Test 6a	0.8487	1	0.3569