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Hexamethylenediamine

CAS Registry Number: 124-09-4

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Revision History

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
A	animal
ACGIH	American Conference of Governmental Industrial Hygienists
°C	degrees centigrade
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Response Software
BMR	benchmark response
BW	body weight
C	concentration
CAS	Chemical Abstracts Service
CIIT	Chemical Industry Institute of Toxicology
cm	centimeter
cm^2	centimeter squared
cm^3	centimeter cubed
d	day(s)
DF	deposition fraction
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

Acronyms and Abbreviations	Definition
$^{chronic}ESL_{threshold(c)}$	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	extra thoracic
g	gram(s)
GD	gestational day
GSD	geometric standard deviation (σ_g)
H	human
h	hour
HEC	human equivalent concentration
HDDC	hexamethylenediamine dihydrochloride
Hg	mercury
HMDA	hexamethylenediamine
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
kg	kilogram
Kow	Octanol/water partition coefficient
L	liter
LOAEL	lowest-observed-adverse-effect-level
$LOAEL_{HEC}$	LOAEL adjusted for human equivalent concentration
LOEL	lowest-observed-effect-level

Acronyms and Abbreviations	Definition
µg	microgram
µg/m^3	micrograms per cubic meter of air
µm	micrometer
m^3	cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute
ml	milliliter
mm	millimeter
MMAD	mean mass aerodynamic diameter
MOA	mode of action
MPPD	multiple path particle dosimetry
nd	not determined
NF	normalizing factor
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
pKa	acid dissociation constant
PM_{10}	particulate matter ≤ 10 µm in diameter
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
RDDR	regional deposited dose ratio

Acronyms and Abbreviations	Definition
ReV	reference value
RfC	Reference Concentration
RIVM	National Institute for Public Health and the Environment
SIDS	Screening Information Data Set
T	time
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TSCA	Toxic Substances Control Act
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
URF	unit risk factor
USEPA	United States Environmental Protection Agency
VE	minute volume
VE_h	default non-occupational ventilation rate for a 24-h day (20 m^3/day)
wk	week(s)

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of hexamethylenediamine (HMDA). 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 HMDA's physical/chemical data. The derivation of the chronic ReV for HMDA has been published (Myers and Grant 2015).

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV	**Short-Term Health** [b] **54 µg/m^3 (PM_{10})**	**Critical Effect**: Inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa in F344/N rats
$^{acute}ESL_{odor}$	**Odor 370 µg/m^3**	Pungent, ammonia-like; weak fishy odor. Triethylamine odor-based value used as a surrogate
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	**Long-Term Health** [b] **1.8 µg/m^3 (PM_{10})**	**Critical Effect(s)**: Hyaline degeneration of olfactory and respiratory epithelium in the nasal passages of mice
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Not likely to be carcinogenic to humans via the inhalation route
$^{chronic}ESL_{veg}$	- - -	No data found

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

[b] Values apply to respirable HMDA ≤ 10 µm in diameter (PM_{10})

Table 2. Air Permitting Effects Screening Levels (ESLs)

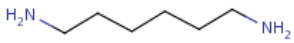
Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	**Short-Term ESL for Air Permit Reviews [a,c] 16 µg/m^3 (PM_{10})**	**Critical Effect**: Inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa in F344/N rats
$^{acute}ESL_{odor}$	**Odor 370 µg/m^3**	Pungent, ammonia-like; weak fishy odor. Triethylamine odor-based value used as a surrogate
$^{acute}ESL_{veg}$	- - -	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**Long-Term ESL for Air Permit Reviews [b,c] 0.54 µg/m^3 (PM_{10})**	**Critical Effect(s)**: Hyaline degeneration of olfactory and respiratory epithelium in the nasal passages of mice
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Not likely to be carcinogenic to humans via the inhalation route
$^{chronic}ESL_{veg}$	- - -	No data found

[a] Based on the acute ReV of 54 µg/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[b] Based on the chronic ReV of 1.8 µg/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review

[c] Values apply to respirable HMDA ≤ 10 µm in diameter (PM_{10})

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C6H16NH2	ACGIH 2001
Chemical Structure		ChemIDplus Lite [a]
Molecular Weight	116.21	ACGIH 2001
Physical State at 25°C	solid	ACGIH 2001
Color	White crystalline	ACGIH 2001
Odor	Ammonia-like; weak fishy odor	ACGIH 2001
CAS Registry Number	124-09-4	ACGIH 2001
Synonyms	1,6-Diamino-n-hexane, 1,6-Diaminohexane, 1,6-Hexanediamine, 1,6-Hexylenediamine, HMDA	ChemIDplus Lite [a]
Solubility in water	2,460,000 mg/L	ChemIDplus Lite [a]
Log K_{ow}	0.35	ChemIDplus Lite [a]
Density (water = 1)	0.848	MSDS sheet Fisher [b]
Vapor Pressure	3 mm Hg @ 60°C	ACGIH 2001
Melting Point	40.9 °C	ACGIH 2001
Boiling Point	204.5 °C	ACGIH 2001
Conversion Factors	1 ppm = 4.74 mg/m^3 1 mg/m^3 = 0.21 ppm	ACGIH 2001

[a] accessed July 7, 2014

[b] accessed May 23, 2013

Chapter 2 Major Sources and Uses

HMDA belongs to the diamines chemical class. Generally, diamines are used industrially as corrosion inhibitors; as curing agents for epoxide resins and plastic articles; as chemical intermediates in the manufacture of resins (polyamide and nylon); and for printing inks, paints and textiles (ACGIH 2001).

Kennedy (2005) reviewed the toxicity of HMDA and provided the following additional information:

> HMDA is used extensively in the fiber and plastics industry as a basic intermediate in the production of nylon, high-strength resins, boiler feedwater additives, and polyamide adhesives. HMDA is one of the monomers used in the production of nylon 6,6. It is used in polymers approved for food contact applications including dimerized with vegetable oil acids producing polyamide adhesives, polyamides for use in side seam cements, formulation of fine contact nylon resins, and in condensation polymers with terephthalic and isophthalic acid for contact with foods except in beverages with more than 8% alcohol.

The estimated production of HMDA by DuPont USA was 227,000 to 454,000 tons/year in 1993 (OECD SIDS, year not determined (nd)). Release into the environment through different waste streams may occur due to HMDA's production and use as a chemical intermediate in the production of nylon-type polyimide resins (HSDB 2013).

HMDA 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 HMDA concentrations in Texas ambient air.

Chapter 3 Acute Evaluation

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

HMDA is a respiratory irritant whose effects occur primarily in the upper respiratory tract. Systemic effects have not been noted except at high concentrations. HMDA is considered to be moderately toxic (Kennedy 2005).

3.1.1 Physical/Chemical Properties

HMDA is a white crystalline solid. Under environmental conditions, HMDA exists in an ionic state (+2). Its odor has been described as ammonia-like by ACGIH (2001) or as a weak, fishy odor by Kennedy (2005). It is very soluble in water and slightly soluble in alcohol and benzene. The log Kow of 0.35 is low and indicates it is unlikely to bio-concentrate. HMDA has a low vapor pressure, so the likelihood of significant vapor exposure is limited unless HMDA is heated (Johannsen et al. 1987). Other physical/chemical properties of HMDA can be found in Table 3.

3.1.2 Key and Supporting Studies

3.1.2.1 Human Studies

There are limited human studies. There are no human studies with adequate exposure information for toxicity factor development. At least two incidents involving HMDA poisoning in humans have been described in the literature. At an Italian nylon manufacturing plant, 20 workers were exposed to HMDA and adiponitrile in air at concentrations ranging from 2 to 5.5 mg/m^3 during normal plant operations and from 32.7 to 131.5 mg/m^3 during autoclaving. Irritation of the conjunctiva and respiratory tract was reported in 8 workers; 1 worker developed contact dermatitis and acute hepatitis, which were believed to be due to HMDA exposure. No anemia was seen in any of the workers (Ceresa 1948; Gallo and Ghiringhelli 1958).

Another group of workers were exposed to HMDA in an epoxide resin plant. A variety of symptoms, including itching, allergic rhinitis, bronchial asthma, impairment of bronchial permeability, toxicoallergic hepatitis, gastritis, colitis, hypergammaglobulinemia, increased serum transaminase activity, and eosinophilia of peripheral blood, were reported after prolonged contact. This was noted within a group of 488 workers (Gul'ko 1971).

3.1.2.2 Key Animal Study - Hébert et al. (1993)

The US National Toxicology Program (NTP 1993) exposed F344/N rats and B6C3F1 mice (five males and five females/group, 6-7 weeks of age) by inhalation to aerosols (mean mass aerodynamic diameter (MMAD) = 1.72 µm; geometric standard deviation (GSD) = 1.53) of the dihydrochloride salt of HMDA (hexamethylenediamine dihydrochloride, HDDC, CAS 6055-52-3) for 6 hours/day (h/d), 5 days/week (d/wk), for 12 d in a 16-d period. HDDC is formed by neutralizing HMDA with hydrochloric acid and its use allowed the detection of any specific toxicity associated with HDMA while avoiding the causticity, palatability, and stability problems that would be encountered with the use of HMDA (Hébert et al. 1993). The main conclusions from the NTP (1993) study were published by Hébert et al. (1993).

The use of HDDC instead of HMDA in the NTP study (1993) was justified for several reasons outlined in the study:

- HMDA solutions are highly basic and, as such, are extremely caustic. HMDA has a very high pKa (10.7) and would become protonated very rapidly upon contact with tissues or fluids at physiologic pH, causing local necrosis.
- HMDA strongly absorbs carbon dioxide from the atmosphere. Stability studies conducted by the NTP indicated that under inhalation exposure conditions, HMDA tended to deposit on the walls of the inhalation chambers and become converted to the carbamate form. HDDC was found to be much more stable in the aerosol form than HMDA.

- HDDC has the same organic backbone as HMDA and its use would allow detection of any specific toxicity associated with that backbone while avoiding the causticity, palatability, and stability problems that would be encountered with the use of HMDA.

In addition, the use of the dichloride salt of amines has been used to investigate the toxicity of methylamine, octylamine, and methoxypropylamine (OECD 2011) as well as dimethyamine, diethylamine, dibutylamine, and dipentylamine (OECD 2013).

The two-week study was a range-finding study to determine exposure concentrations for a 13-week study (Section 4.1.2). Hébert et al. (1993) evaluated mean body weights, gross and histopathologic examinations, and clinical pathology of both rats and mice following exposure to several inhalation doses of HDDC. However, data on histopathologic results were not included in the report, only a brief discussion of results. Therefore, benchmark concentration (BMC) modeling could not be conducted.

Rats and mice were exposed to mean concentrations of HDDC, as shown in Table 4. Mean concentrations of HDDC in test atmospheres were within 6% of target levels in both the rat and mice studies. Table 4 compares concentrations of HDDC to calculated equivalent concentrations of HMDA for comparison to supporting studies that exposed animals to HMDA (3.1.2.3 Supporting Studies and Table 6). The molecular weight of HMDA is 116.20 g/mol, while the molecular weight of HDDC is 189.13 g/mol. The ratio of these can be used to determine the percent of HMDA per mg/m^3 of HDDC by weight, allowing for the calculation of the equivalent concentration.

116.20 g/mol / 189.13 g/mol = 0.614 = 61.4%

This percentage reflects that HDDC is made up of 61.4% HMDA and 38.6% dihydrochloride salt. The calculation for conversion would then be:

HDDC (mg/m^3) x 61.4% = HMDA (mg/m^3)

Table 4. HDDC and equivalent concentrations of HMDA

HDDC mg/m^3 [a]	0	10	30	89	267	800
HMDA mg/m^3 [b]	0	6.1	18	55	164	491

[a] analytical concentrations relevant to the Hébert et al. (1993) study

[b] calculated concentrations relevant to the Hébert et al. (1993) study

3.1.2.2.1 Rat Study

Statistical analysis of histopathologic changes was not reported in the NTP study. Therefore, if an effect was noted in the study, it was generally conservatively assumed to be adverse. The following adverse effects were observed in the rat study:

- When rats of both sexes were exposed to 800 mg/m^3 HDDC, they either died or had to be sacrificed due to a moribund condition prior to scheduled termination. Clinical signs of toxicity such as dyspnea, rales, nasal discharge, hypoactivity, diarrhea, and ocular discharge were noted in rats at this concentration. Microscopic changes occurred in lymphatic tissue, the nasal and laryngeal mucosa, the pancreas, and the ovary.
- The body weights of male and female rats exposed to 267 mg /m^3 were less than those of controls, although this difference was not statistically significant. Clinical signs of toxicity were not observed. The incidence and severity of the lesions in rats exposed at 267 mg/m^3 were similar to rats exposed to 800 mg/m^3 HDDC.
- Nasal lesions were present in both males and females at exposure levels of 89 mg/m^3 and greater. Microscopic changes included focal areas of inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa. Degeneration characterized by thinning (atrophy) and necrosis of the olfactory and respiratory epithelium was frequently associated with areas of inflammation and ulceration.
- In the larynx, there were focal areas of inflammation and necrosis with ulceration of laryngeal epithelium at exposure levels as low as 10 mg/m^3 in males and 89 mg/m^3 in females.

The lowest dose where effects were observed (inflammation and necrosis with ulceration of laryngeal epithelium) was 89 mg/m^3 HDDC in female rats and 10 mg/m^3 in male rats. Due to the observed difference in response between the sexes, and as there were no statistical data provided, these results were compared to the results from the 13-wk study published by the same group to inform selection of the lowest observed adverse effect level (LOAEL). In the subchronic study, larynx inflammation was observed in some control animals, and treatment-related effects were only observed at exposure concentrations higher than 50 mg/m^3 (Table 5).

Table 5. Incidence (severity) of larynx histopathologic lesions in rats following a 13-wk exposure

Dose HDDC	**0 mg/m^3**	**1.6 mg/m^3**	**5.0 mg/m^3**	**16 mg/m^3**	**50 mg/m^3**	**160 mg/m^3**
Dose HMDA	**0 mg/m^3**	**0.98 mg/m^3**	**3.1 mg/m^3**	**9.8 mg/m^3**	**31 mg/m^3**	**98 mg/m^3**
Inflammation Males (10 rats)	1 (2.0) [a]	0	0	0	2 (1.0)	7 (1.4)
Inflammation Females (10 rats)	2 (2.0)	0	0	0	0	5 (2.6)
Erosion/ulceration Males (10 rats)	0	0	0	0	0	2 (2.0)
Erosion/ulceration Females (10 rats)	0	0	0	0	0	4 (2.0)
Hyperplasia Males (10 rats)	0	0	0	0	0	1 (1.0)
Hyperplasia Females (10 rats)	0	0	0	0	0	1 (3.0)

[a] Severity score ( ) is based on a scale of 1 to 4: 1, minimal; 2, mild; 3, moderate; 4, marked. Severity scores are averages based on the number of animals with lesions from each group.

After a 13-week exposure (refer to Section 4.1 for details), the following was observed:

- There were no effects observed at 16 mg/m^3 in males or females and the only effect observed at 50 mg/m^3 was a minimal increase in the incidence of inflammation in the larynx of male rats;
- control animals demonstrated mild laryngeal inflammation; and
- there were no consistent differences in effects in the larynx between male and female rats.

The results from the subchronic study in regard to larynx effects suggest that the observations in the acute study for male rats at 10 mg/m^3 are unlikely to actually represent adverse effects. That is, a review of histopathologic lesions in the larynx from the longer 13-wk exposure does not support a LOAEL of 10 mg/m^3 in the acute study for adverse larynx effects in male rats. Therefore, using data from the subchronic study to support selection of a LOAEL from the acute study, nasal lesions were used as the critical end point. The associated LOAEL is 89 mg/m^3 for HDDC with a no observed adverse effect level (NOAEL) of 30 mg/m^3 HDDC for both sexes. This corresponds to a LOAEL of 55 mg/m^3 and a NOAEL of 18 mg/m^3 for HMDA (calculated).

3.1.2.2.2 Mouse Study

Statistical analysis of histopathologic changes was not reported in the NTP study. Therefore, if an effect was noted in the study, it was generally conservatively assumed to be adverse. The following adverse effects were observed in the mouse study:

- At 800 mg/m^3 HDDC, morbidity and mortality occurred in exposed mice of both sexes. Clinical signs of toxicity included dyspnea, rough hair coat, abnormal posture, and hypoactivity. At the end of exposure, the mean body weights of male and female mice were slightly depressed relative to controls. Microscopic changes in mice included lesions in lymphatic tissue, nasal cavity, trachea, larynx, pancreas, testis, and ovary. The only chemical-related gross finding was a small spleen in male and female mice. In the larynx and trachea, focal areas of inflammation and necrosis with ulceration of the respiratory mucosa were present at the two highest exposure levels (267 and 800 mg/m^3).

- Mice exposed at 267 mg/m^3 also exhibited ulceration of the mucosa, acute inflammation, and atrophy of the neural or respiratory epithelium in the nose and nasal cavity.

- Female mice exposed at 30, 89, or 267 mg/m^3 and male mice exposed at 30 or 800 mg/m^3 showed a slight depression in body weight gain relative to controls.

The LOAEL from the mouse study was 267 mg/m^3 with a NOAEL of 89 mg/m^3 (corresponding to a NOAEL for HMDA of 55 mg/m^3). The critical effects in mice were based on ulceration, inflammation and atrophy of the neural or respiratory epithelium in the nose and nasal cavity. The mouse LOAEL and NOAEL values are higher than those observed in the rat in this study.

3.1.2.3 Supporting Studies

A comparison of relevant supporting inhalation studies, discussed below, to the key study (Hébert et al. 1993) is shown in Table 6.

3.1.2.3.1 Monsanto (nd)

Monsanto (nd, as cited in Kennedy 2005) exposed groups of rats to either 49 or 262 mg/m^3 of HMDA dust, 6 h/d, 5 d/wk, for 4 weeks. Sneezing, rhinitis, and rattled breathing were reported at 262 mg/m^3 in addition to discolored fur, ear and tail lesions, and depressed weight gain. At 49 mg/m^3, no evidence of target organ toxicity was observed, but the rats exhibited ruffed fur, ptosis, and hypoactivity. The LOAEL from this study was 49 mg/m^3. This study was not considered as a basis for an acute ReV, as limited information on study quality was available. However, this LOAEL is very similar to the LOAEL of 55 mg/m^3 from the key study.

3.1.2.3.2 Gage (1970)

Gage, (1970) reported results of inhalation toxicity in 109 chemicals, including HMDA. Groups of eight rats each were repeatedly exposed to nominal concentrations of 1,000, 5,000, or 10,000 mg/m^3 HMDA for 6 h/d. The results are as follows:

- In rats exposed to 10,000 mg/m^3, three rats died after two exposures. The survivors exhibited nasal irritation, respiratory difficulty, and lethargy. Autopsy showed lung congestion, peribronchiolar inflammation, areas of hemorrhage and edema in the lungs, and vacuolation of kidney tubules.
- One of 10 rats exposed 11 times to 5,000 mg/m^3 died. Clinical signs of toxicity included lung and nasal irritation, reduced weight gain, and lethargy. Urine and blood tests were normal. Autopsy revealed petechial hemorrhage in the lungs and lung inflammation.
- No toxic or pathological signs were observed in rats exposed 15 times to 1,000 mg/m^3.
- The NOAEL from the Gage (1970) study was 1,000 mg/m^3.

This study was not considered for the development of an acute ReV because of the quality of the study, the low number of animals tested, nominal rather than analytical concentrations were reported, and the availability of better conducted studies.

3.1.2.3.3 Standard Oil (nd)

As cited in Kennedy (2005), ten guinea pigs were exposed by inhalation to 237 mg/m^3 HMDA for 2-h exposure periods for 3 d. All the animals were dead after 3 to 4 d of exposure. The guinea pigs exhibited general weakness and impairment of appetite. Alertness and reaction to stimuli were markedly reduced. Dyspnea was noted in all exposed guinea pigs with severity progressing with prolongation of exposure. No pathological changes were observed (Standard Oil, nd). This study was not considered for the development of an acute ReV because of the severity of the end points observed, use of only one dose group, limited details on study quality, etc.

Table 6. Subacute inhalation studies

Exposure Concentration (Species)	**Exposure (Number/sex/ dose)**	**NOAEL**	**LOAEL**	**Notes (References)**
0, 10, 30, 89, 267, 800 mg/m^3 HDDC (**0, 6.1, 18, 55, 164, 491 mg/m^3 HMDA**) [c] (Rat)	6 h/d; 5 d/wk; 12 d over a 16 d period (5 M, 5 F per exposure group)	30 mg/m^3 HDDC (**18 mg/m3 HMDA**)	89 mg/m^3 HDDC (**55 mg/m^3 HMDA**) Inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa	Mortality at 800 mg/m^3 HDDC (**491 mg/m^3 HMDA**); inflammation and ulceration of the nasal cavity at 267 mg/m^3 HDDC (**164 mg/m^3 HMDA**) (Hébert et al. 1993) [a]
0, 10, 30, 89, 267, 800 mg/m^3 HDDC (**0, 6.1, 18, 55, 164, 491 mg/m^3 HMDA**) (Mouse)	6 h/d; 5 d/wk; 12 d over a 16 d period (5 M, 5 F per exposure group)	89 mg/m^3 HDDC (**55 mg/m^3 HMDA**)	267 mg/m^3 HDDC (**164 mg/m^3 HMDA**) Ulceration, inflammation and atrophy of the neural or respiratory epithelium in the nose and nasal cavity	Mortality at 800 mg/m^3 HDDC (**491 mg/m^3 HMDA**); (Hébert et al. 1993)
49 and 262 mg/m^3 (Rat)	6 h/d; 5 d/wk; 4 wk (unspecified)	- - -	49 mg/m^3 ruffled fur, ptosis, and hypoactivity	At 262 mg/m^3, sneezing, rhinitis, and rattled breathing as well as discolored fur, ear and tail lesions, and depressed weight gain occurred Unpublished data (Monsanto nd) [b]
1,000, 5,000, 10,000 mg/m^3 (Rat)	15 exposures in 3 wk for the 1,000 mg/m^3 group (4M 4F)	1,000 mg/m^3	5,000 mg/m^3 Reduced weight gain, 1/11 mortality, respiratory tract irritation	Mortality at 10,000 mg/m^3 (Gage 1970) [b]
237 mg/m^3 (Guinea pig)	2 h/d; 3-4 d	- - -	237 mg/m^3 mortality	Unpublished data (Standard Oil Co. nd) [b]

[a] Key Studies

[b] Limited data on study quality

[c] Calculated concentrations, see Table 4 and Section 3.1.2

3.1.2.4 Reproductive/Developmental Studies

The majority of reproductive/developmental animal studies were conducted via the oral route of exposure. NTP (1993) evaluated reproductive effects in rats and mice via inhalation for 13 weeks. These studies are discussed in Section 4.1.2.2. All mating, gestational and lactational parameters were considered normal, and no effects were identified that could be attributed to exposure to HDDC (Hébert et al. 1993). In the following oral or i.p. studies, reproductive/ developmental effects only occurred at high dose and acute exposures during critical windows of development (Johannsen and Levinskas 1987; David and d'A. Heck 1983)

3.1.2.4.1 Johannsen and Levinskas (1987)

Johannsen and Levinskas (1987) administered 112, 184, or 300 mg/kg of HMDA via the oral route of exposure on gestational days (GD) 6–15 to groups of 22 pregnant rats. Most of the effects were observed at the two highest doses, 184 and 300 mg/kg HMDA:

- A single death and one sacrificed rat in a moribund condition were considered to have resulted from HMDA treatment in the 300 mg/kg group. Transient reductions in food consumption were noted. Thus, pregnant rats gained less weight than controls throughout the test period, and statistically significant differences were observed through GD 15 and again on day 21 after adjustment for fetal, uterine and placental weights. A significant decrease in fetal body weights of both male and female pups was observed. Visceral examinations revealed a significant increase in the number of pups with spotty livers in the high-dose group.
- The occurrence of fetuses with poorly or unossified cervical centra or sacral/caudal vertebra indicates a slight retardation in skeletal development observed at both the 184 and 300 mg/kg dose levels.
- No maternal toxicity was noted at either 112 or 184 mg/kg. No significant effects in fetuses occurred at 112 mg/kg.

In a pilot for the above study, 4 to 6 pregnant rats were administered 112.5, 225, 450, or 900 mg/kg of HMDA via the oral route of exposure on GD 6–15. Severe adverse effects (mortality and severe internal hemorrhaging) were observed in all dams at the two highest dose groups. Reduced body weight gains were observed in dams administered 225 mg/kg, whereas no effects were noted in dams administered 112.5 mg/kg. Neither embryotoxicity, fetotoxicity, nor external malformations were apparent up to 225 mg/kg per day (Johannsen and Levinskas, 1987).

Thus, the NOAEL for maternal toxicity was 184 mg/kg and the NOAEL for fetal toxicity was 112.5 mg/kg. Using route-to-route extrapolation (assuming 100% absorption), the fetal NOAEL of 112.5 mg/kg was converted to an inhalation exposure:

$$NOAEL_{inhaltion} = NOAEL_{oral} \times (BW/VE_h)$$

BW = default human body weight (70 kg)

VE_h = default non-occupational ventilation rate for a 24-h day (20 m^3/day)

$NOAEL_{inhalation}$ = 112.5 mg/kg x (70 kg / 20 m^3/day) = 394 mg/m^3

The resulting inhalation NOAEL would be 394 mg/m^3. At this concentration, severe respiratory effects might occur in exposed animals.

3.1.2.4.2 David and Heck (1983)

As cited in NTP (1993) and Kennedy (2005), David and Heck (1983) treated pregnant rats with doses of 10, 100, and 200 mg/kg HMDA by gavage on days 0 to 14 of gestation. No effects on the number of fetuses, resorptions, or corpora lutea occurred. In the dams administered the highest dose, a significant decrease in weight gain occurred in the dams.

3.1.2.4.3 Manen et al. (1993) and Monsanto (nd)

In studies by Manen et al. (1993) and Monsanto (nd), both cited in Kennedy (2005), pregnant mice were given HMDA via i.p. injection during days 10 to 14 of gestation (the time of maximal fetal ornithine decarboxylase activity). An inhibition of fetal ornithine decarboxylase activity was observed 2 h later, and a proportional decrease in fetal weight was observed on day 18 of gestation (Manen et al., 1983). An i.p. injection of 103 mg/kg of HMDA to pregnant mice, 4 times/d on days GD 10–14, resulted in retarded fetal-skeletal development and retarded weight gain (Monsanto, nd).

3.1.2.4.4 Conclusions about potential reproductive and developmental effects

HMDA is a moderate point-of-contact respiratory irritant and is assumed to be efficiently scrubbed in the upper respiratory tract. At low concentrations that protect against mild respiratory irritation, there would be insignificant distribution remote to the respiratory tract, so reproductive/developmental effects would not be expected at concentrations that protect against respiratory effects.

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

HMDA is corrosive and strongly alkaline, with a pKa of 10.7. When HMDA comes in contact with tissues or fluids at physiologic pH, it becomes protonated, causing local necrosis. It is irritating to the skin and mucous membranes (NTP 1993). Therefore, the exposure concentration of the parent chemical was used as the dose metric.

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

Since the NOAEL in rats was 30 mg/m^3 and the NOAEL in mice was 89 mg/m^3 (approximately a factor of 3 difference), both the rat and mouse results from the key study of Hébert et al. (1993) were considered in identifying the critical effects for the acute ReV. The potential critical effects are inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa

(both rats and mice) and atrophy of the neural or respiratory epithelium in the nose and nasal cavity (mice). BMC modeling was not conducted because neither NTP (1993) nor Hébert et al. (1993) provided detailed histopathology results.

3.1.5 Dosimetric Adjustments

Dosimetric adjustments were made on the NOAELs of 30 mg/m^3 HDDC for rats and 89 mg/m^3 for mice.

3.1.5.1 Default Exposure Duration Adjustments

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

$$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$

Rat study:

$$POD_{ADJ} = [(30 \text{ mg/m}^3)^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 54.5136 \text{ mg/m}^3$$

Mouse study:

$$POD_{ADJ} = [(89 \text{ mg/m}^3)^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 161.7237 \text{ mg/m}^3$$

3.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

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

Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions considered. The mean mass median aerodynamic diameter (MMAD) for each chamber ranged from 1.62 – 1.72 µm with a geometric standard deviation (GSD) of 1.52 to 1.53 (Hébert et al. 1993). For the MPPD model, the high end was used for both parameters (MMAD = 1.72 µm; GSD = 1.53). The particle density for HDDC is not known, so a default value of 1 g/cm^3 was used.

For the regional deposited dose ratio (RDDR) calculations, the TD used the default minute ventilation (VE) for humans (13,800 mL/min) given by USEPA (1994). Neither USEPA (1994)

nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TD used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model. The calculated human tidal volume is 842.74 ml/breath and the breathing frequency is 16.375 breaths per minute. Except for the parameter values discussed above, all remaining values used were default (refer to Appendix 1).

3.1.5.2.1 Rat Study

For the rat study, the minute volume was calculated based on the body weight for males (198 grams) and females rats (134 grams) observed in the study for exposure at 30 mg/m^3 (the NOAEL). The average body weight was 166 grams and the calculated minute volume was 128.4359 mL/min (USEPA 1994). The chemical concentration is the POD_{ADJ} of 54.5136 mg/m^3. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). The head/extrathoracic surface areas for humans (200 cm^2) and rats (15 cm^2) used as the normalizing factors were taken from the EPA RfC guidance (USEPA 1994). Once the deposition fractions for the rat (DF_A = 0.5375) and human (DF_H = 0.4562) were determined (Appendix 2), the RDDR was calculated as follows:

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

where: V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor (extrathoracic surface areas)
A = animal
H = human

$$RDDR = [128.4359 \text{ mL/min} / 13{,}800 \text{ mL/min}] \times [0.5375/0.4562] \times [200 \text{ cm}^2/15 \text{ cm}^2]$$

$$RDDR = 0.1462$$

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD (POD_{HEC}).

$$POD_{HEC} \text{ for HDDC} = POD_{ADJ} \times RDDR = 54.5136 \text{ mg/m}^3 \times 0.1462 = 7.9699 \text{ mg/m}^3$$

3.1.5.2.2 Mouse Study

The final body weight of the mice at 89 mg/m^3 HDDC was 26.2 g for males and 20.6 g for females (Hébert et al. 1993). There were no consistent differences in the response between males and females exposed to HDDC, so the average body weight of 23.4 g was used. The calculated minute volume was 26.8693 mL/min (USEPA 1994). The chemical concentration is the POD_{ADJ} of 161.7237 mg/m^3. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). The head/extrathoracic surface areas for humans (200 cm^2) and mice (3 cm^2) used as the normalizing factors were taken from the EPA RfC guidance (USEPA 1994). Once the deposition fractions for the mouse (DF_A = 0.4938) and human (DF_H = 0.4562) were determined (Appendix 2), the RDDR was calculated as follows:

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

where: V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor (extrathoracic surface areas)
A = animal
H = human

$$RDDR = [26.8693 \text{ mL/min} / 13{,}800 \text{ mL/min}] \times [0.4938/0.4562] \times [200 \text{ cm}^2/3 \text{ cm}^2]$$

$$RDDR = 0.1405$$

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD (POD_{HEC}).

$$POD_{HEC} \text{ for HDDC} = POD_{ADJ} \times RDDR = 161.7237 \text{ mg/m}^3 \times 0.1405 = 22.7222 \text{ mg/m}^3$$

3.1.5.3 Comparison of the Calculated Rat and Mouse POD_{HEC}

The following POD_{HEC} values were determined using the data from Hébert et al. (1993):

Rat: POD_{HEC} = 7.9699 mg/m^3

Mouse: POD_{HEC} = 22.7222 mg/m^3

3.1.6 Adjustments of the POD_{HEC} by Uncertainty Factors

The POD_{HEC} values above are based on NOAELs, although the LOAEL-based values would differ to a similar degree. As the rat LOAEL-based POD_{HEC} would be lower than that for the mouse, critical effects (i.e., based on the POD_{HEC}, the first adverse effects which may appear in humans as dose increases) are based on the rat. Thus, the lowest POD_{HEC} of 7.9699 mg/m^3 was selected for the most sensitive species and based on the rat study by Hébert et al. (1993). Inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa is

assumed to have a threshold. The default for noncarcinogenic 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} of 7.9644 mg/m^3: 10 for intraspecies variability (UF_H), 3 for extrapolation from animals to humans (UF_A), and 6 for database uncertainty (UF_D), for a total UF = 90:

- A UF_H of 10 was used to account for variation in sensitivity among the members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences.
- A UF_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 reduced UF_D of 3 was used because the Hébert et al. (1993) study was considered a medium quality study because only 5 males and 5 females of each sex were evaluated and detailed histopathology results were not published. A UF_D of 10 was not used because the 2-wk inhalation study conducted by Hébert et al. (1993) evaluated two different species (mouse and rat), there is some available human data, the MOA is relevant to humans, and there are several animal reproductive and developmental studies. Statistical analyses were not conducted, although a conservative assumption was made that if an effect was noted, it was considered adverse. The confidence in the acute database is medium. HMDA is not considered a reproductive/developmental toxicant based on oral and inhalation studies.

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_D)$$
$$= 7.9699 \text{ mg/m}^3 / (10 \times 3 \times 3)$$
$$= 7.9699 \text{ mg/m}^3 / 90$$
$$= 0.08855 \text{ mg/m}^3$$
$$= 88.55 \text{ µg/m}^3$$

3.1.7 Conversion from HDDC to HMDA

In the key study, HDDC was used as the test chemical rather than HMDA. Therefore, the acute ReV was initially calculated for HDDC and then adjusted for HMDA.

acute ReV for HDDC = 88.55 µg/m^3

HDDC is 61.4% by weight HMDA (calculated from the molecular weight)

Therefore the acute ReV of HMDA = 61.4/100 x 88.55 µg/m^3

= 54.37 µg/m^3

= 54 µg/m^3 (rounded to 2 significant figures)

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

The acute ReV was rounded to two significant figures. The resulting 1-h acute ReV is 54 µg/m^3 (for PM_{10}). 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 16 µg/m^3 (for PM_{10}) (Table 7).

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

Parameter	**Summary**
Study	2-wk study in F344/N rats and B6C3F1 mice (Hébert et al. 1993)
Study population	F344/N rats, most sensitive species (5 males and 5 females per dose)
Study quality	Medium
Exposure methods	Exposures via inhalation to HDDC aerosol (MMAD = 1.72 µm; GSD = 1.53) at 10, 30, 89, 267, and 800 mg/m^3 [a]
Critical effects	Inflammation and ulceration in both respiratory and olfactory portions of the nasal mucosa in F344/N rats
POD for observed adverse effect level (LOAEL)	89 mg/m^3 HDDC
POD (NOAEL)	30 mg/m^3 HDDC
Exposure duration	6 h/d for 12 d over a 16-d period
Extrapolation to 1 h	Haber's rule with n = 3
POD_{ADJ} (1 h)	54.5136 mg/m^3 HDDC
POD_{HEC}	7.9699 mg/m^3 HDDC
Total uncertainty factors (UFs)	90
Interspecies UF	10
Intraspecies UF	3
Incomplete Database UF *Database Quality*	3 Medium
acute ReV [1 h] (HQ = 1) HDDC	88.55 µg/m^3
acute ReV [1 h] (HQ = 1) HMDA	**54 µg/m^3 (PM_{10})**
^{acute}ESL [1 h] (HQ = 0.3)	**16 µg/m^3 (PM_{10})**

[a] Hébert et al. (1993) exposed rodents to HDDC (0, 6.1, 18, 55, 164, 491 mg/m^3 HMDA)

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Nonneutralized HMDA solutions have a pungent odor (NTP 1993). The odor of HMDA has been described as ammonia-like (ACGIH 2001) or as a weak, fishy odor (Kennedy 2005). Kulakov (1964) reported that the "olfactory threshold" of HMDA was 0.68 ppb; however, the quantitation of exposure concentrations was questionable, and the term "olfactory threshold" was not defined. Since HMDA has a pungent odor, an $^{acute}ESL_{odor}$ of 370 µg/m^3 was set for HMDA based on the $^{acute}ESL_{odor}$ for triethylamine, a structurally similar amine (TCEQ 2015b).

3.2.2 Vegetation Effects

No data were found regarding short-term vegetative 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 = 54 µg/m^3
- $^{acute}ESL$ = 16 µg/m^3
- $^{acute}ESL_{odor}$ = 370 µg/m^3

The short-term ESL for air permit evaluations is the $^{acute}ESL$ of 16 µg/m^3 (PM_{10}) (Table 2).

3.4. Acute Inhalation Observed Adverse Effect Level

The LOAEL value of 89 mg/m^3 determined in rats, the most sensitive species, from the Hébert et al. study (1993) (Tables 6 and 7) was used as the POD for calculation of an acute inhalation observed adverse effect level. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. No duration adjustment was made (TCEQ 2015a). However, an animal-to-human dosimetric adjustment was made to calculate a $LOAEL_{HEC}$:

For aerosols, the $LOAEL_{HEC}$ was calculated using the following equation:

$LOAEL_{HEC}$ = LOAEL x $RDDR_{ET}$ (Section 3.1.5.2)
= 89 mg/m^3 HDDC x 0.1462
= 13.01 mg/m^3 HDDC x 61.4/100
(conversion from HDDC to HMDA, see section 3.1.7)
= 7.988 mg/m^3 HMDA
= 8.0 mg/m^3 (rounded to two significant figures)

The $LOAEL_{HEC}$ determined from animal studies, where effects occurred in some animals, represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The acute inhalation observed adverse effect level of 8 mg/m^3 is provided for informational purposes only (TCEQ 2015a). The margin of exposure between the acute inhalation observed adverse effect level of 8 mg/m^3 to the ReV of 0.054 mg/m^3 is a factor of nearly 150.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Even after chronic exposure, HMDA is a respiratory irritant whose effects occur primarily in the upper respiratory tract. Systemic effects were not noted except at high concentrations (similar to acute effects). There are no published epidemiology studies or reports of health effects in humans with adequate HMDA exposure data, except as discussed in Section 3.1.2.2. Therefore, animal studies were used for the chronic ReV.

4.1.1 Physical/Chemical Properties

The log K_{ow} of 0.35 is low and indicates it is unlikely to bio-concentrate. For other physical/chemical properties, refer to Section 3.1.1 and Table 3.

4.1.2 Key Study and Supporting Studies

4.1.2.1 Key Animal Study - Hébert et al. (1993)

Hébert et al. (1993) exposed F344/N rats and B6C3F1 mice (10 males and 10 females/dose group, 6-7 weeks of age) by inhalation to the HDDC for 6 h/d, 5 d/wk, for 13 wks. Animals were evaluated for histopathology, clinical chemistry, hematology, and reproductive toxicity. In addition, special groups of 20 male and 40 female rats and mice (mating trial animals) at each exposure level were included to assess the effect of HDDC on reproduction (discussed in Section 4.1.2.2). The genetic toxicity of HMDA was assessed in *Salmonella typhimurium* and in Chinese hamster ovary cells *in vitro*. HMDA was evaluated in the mouse micronucleus assay *in vivo* (discussed in Section 4.2, detailed in NTP 1993).

Rats and mice were exposed to mean concentrations of HDDC. Mean concentrations of HDDC in test atmospheres were within 6% of target levels in both the rat and mice studies. Table 8 (below) shows concentrations of HDDC and the calculated equivalent concentrations of HMDA. The following sections report HMDA concentrations as well as HDDC so these results can be compared to other supporting studies.

Table 8. HDDC and Equivalent Concentrations of HMDA

HDDC mg/m^3 [a]	0	1.6	5	16	50	160
HMDA mg/m^3 [b]	0	0.98	3.1	9.8	31	98

[a] analytical concentrations relevant to the Hébert et al. (1993) study

[b] calculated concentrations relevant to the Hébert et al. (1993) study

All rats and mice survived to the end of the studies, and there were no significant exposure-related changes in group mean body weights, clinical signs of toxicity or gross lesions seen in either species.

At 50 and 160 mg/m^3 HDDC, liver weights in male mice were increased slightly and statistically significantly relative to controls. Exposure-related microscopic lesions in male and female rats and mice were limited to the upper respiratory tract (larynx and nasal passages) in the two highest exposure groups and were similar in both species. These lesions included minimal to mild focal erosion/ulceration, inflammation, and hyperplasia of the laryngeal epithelium as well as degeneration of the olfactory and respiratory nasal epithelium. In female rats, a dose-related decrease in white blood cell count was observed. Appendix 3 provides a summary of histopathological changes obtained from Hébert et al. (1993) to the respiratory tract of rats and mice.

The toxicity of HDDC to rats and mice resulted from irritant properties of the chemical and was consistent with the effects of other irritants administered by inhalation. This toxicity was limited to the upper respiratory tract (larynx and nasal passages). In the 13-wk study, the LOAEL and NOAEL are 16 mg/m^3 and 5 mg/m^3 HDDC, respectively, in both rats and mice. Tables 9-11 contain data on histopathologic lesions that occurred at the lowest concentrations in the 13-wk study with an adequate dose-response relationship. The differences between males and females were minimal, so the histopathology results were summed. Benchmark concentration (BMC) modeling was conducted for these data sets and is detailed in Appendix 4.

Table 9. Incidence (Severity) of Respiratory Epithelial Degeneration in the Nose/Nasal Passages in Rats

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Dose HMDA	0 mg/m^3	0.98 mg/m^3	3.1 mg/m^3	9.8 mg/m^3	31 mg/m^3	98 mg/m^3
Males (10 rats)	0	0	0	0	3 (1.0) [a]	10 (2.0)
Females (10 rats)	0	0	0	1 (1.0)	4 (1.2)	8 (1.8)
Sum (20 rats)	0	0	0	1	7	18

[a] Severity score ( ) is based on a scale of 1 to 4: 1, minimal; 2, mild; 3, moderate; 4, marked. Severity scores are averages based on the number of animals with lesions from each group.

Table 10. Incidence (Severity) of Hyaline Degeneration in the Respiratory Epithelium in Mice

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Dose HMDA	0 mg/m^3	0.98 mg/m^3	3.1 mg/m^3	9.8 mg/m^3	31 mg/m^3	98 mg/m^3
Males (10 mice)	0	0	0	1 (1.0) [a]	8 (1.0)	10 (1.8)
Females (10 mice)	0	0	0	0	10 (1.0)	10 (2.0)
Sum (20 mice)	0	0	0	1	18	20

[a] Severity score ( ) is based on a scale of 1 to 4: 1, minimal; 2, mild; 3, moderate; 4, marked. Severity scores are averages based on the number of animals with lesions from each group.

Table 11. Incidence (Severity) Of Hyaline Degeneration in the Olfactory Epithelium in Mice

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Dose HMDA	0 mg/m^3	0.98 mg/m^3	3.1 mg/m^3	9.8 mg/m^3	31 mg/m^3	98 mg/m^3
Males (10 mice)	0	0	0	2 (1.0) [a]	8 (1.0)	10 (2.3)
Females (10 mice)	0	0	0	1 (2.0)	10 (1.0)	10 (2.1)
Sum (20 mice)	0	0	0	3	18	20

[a] Severity score ( ) is based on a scale of 1 to 4: 1, minimal; 2, mild; 3, moderate; 4, marked. Severity scores are averages based on the number of animals with lesions from each group.

The LOAEL for these histological changes was 16 mg/m^3 HDDC (9.8 mg/m^3 HMDA), and the NOAEL was 5 mg/m^3 HDDC (3.1 mg/m^3 HMDA).

4.1.2.2 Supporting Studies

A comparison of relevant supporting inhalation studies to the key study (Hébert et al.1993) is shown in Table 12.

4.1.2.2.1 Johannsen et al. (1987)

Johannsen et al. (1987) treated groups of 15 male and 15 female Sprague-Dawley rats by inhalation 6 h/d, 5 d/wk for 13 wks to aerosols of HMDA at 12.8 and 51 mg/m^3 (analytical concentrations). An additional group of rats was exposed to 215 mg/m^3 but showed exposure-related deaths, so this group was terminated during the seventh week of the study. Clinical laboratory and hematological responses were conducted with body and organ weight measurements followed by histopathology.

- At 215 mg/m^3, body weight gain was significantly reduced in rats of both sexes. After 5 wks of exposure, slight hematopoietic stimulation of peripheral blood parameters was observed in both sexes. Treatment-related microscopic lesions were seen only in rats exposed to 215 mg/m^3 and were confined to the trachea, nasal passages, and lungs
- At 51 and 215 mg/m^3, physical signs of respiratory and conjunctival irritation were noted, but no corresponding microscopic signs of irritation were observed at 51 mg/m^3

The LOAEL for HMDA was 51 mg/m^3, and the NOAEL was 12.8 mg/m^3 based on respiratory and conjunctival irritation. These values are comparable to the LOAEL and NOAEL from the Hébert et al. (1993) study, 9.8 mg/m^3 and 3.1 mg/m^3 HMDA, respectively, making this an appropriate supportive study (Table 12).

Table 12. Subchronic Inhalation Studies

Exposure Concentration (species)	Exposure	NOAEL	LOAEL	Notes (References)
1.6, 5, 16, 50, 160 mg/m^3 HDDC (**0.98, 3.1, 9.8, 31, 98 mg/m^3 HMDA**) (Rat)	13 wks 6 h/d, 5 d/wk	5 mg/m^3 HDDC (**3.1 mg/m^3 HMDA**)	16 mg/m^3 HDDC (**9.8 mg/m^3 HMDA**) irritation of the larynx, olfactory and respiratory nasal epithelium.	Hébert et al. (1993)
1.6, 5, 16, 50, 160 mg/m^3 HDDC (**0.98, 3.1, 9.8, 31, 98 mg/m^3 HMDA**) (Mouse)	13 wks 6 h/d, 5 d/wk	5 mg/m^3 HDDC (**3.1 mg/m^3 HMDA**)	16 mg/m^3 HDDC (**9.8 mg/m^3 HMDA**) irritation of the larynx, olfactory and respiratory nasal epithelium.	Hébert et al. (1993)
12.5, 51, 215 mg/m^3 HMDA (Rat)	13 wks 6 hr/d, 5 d/wk	12.8 mg/m^3	51 mg/m^3 respiratory and conjunctival irritation	At 215 mg/m^3, mortality, body weight reduction, respiratory tract irritation; (Johannsen et al. 1987)

4.1.2.2.2 Other Studies

Kulakov (1964) and Osintseva et al. (1966) conducted subchronic inhalation studies on HMDA. However, only limited information was available for these studies and they were not considered for development of the chronic ReV. Osintseva et al. (1966) exposed rats 24 h/d for 3 months to levels of 0.001, 0.04, and 1.0 mg/m^3 HMDA. Increased hyperemia of the liver, kidney, and

myocardium were observed at 0.04 and 1.0 mg/m^3 HMDA. Preliminary findings from this same study also were reported previously by Kulakov (1964).

4.1.2.3 Reproductive/Developmental Studies

4.1.2.3.1 Hébert et al. (1993)

Reproductive/developmental effects were also investigated in the Hébert et al. (1993) study in the three highest exposure groups: 16, 50, and 160 mg/m^3 HDDC (9.8, 31, and 98 mg/m^3 HMDA). Sperm morphology including sperm motility and density and vaginal cytology evaluations were conducted at necropsy on the rats and mice used in the original 13 wk study (10 male and female rats and mice per group). Additional groups of 20 male and 40 female rats and mice for each of the control and exposure groups were used for mating trials (necropsies were not performed on these animals).

HDDC did not have any adverse effects on reproduction in mice or rats (no effect on fertility, body weights, or body weight gains). HDDC caused no significant changes that were considered adverse in sperm morphology or in the length of the estrous cycle of rats or mice. During the mating trials, three female mice exposed to 16 mg/m^3 and one female and one male mouse exposed to 50 mg/m^3 died before scheduled termination. These deaths, however, were not considered to be related to chemical exposure.

In the 50 mg/m^3 and 160 mg/m^3 exposure groups, the only statistically significant changes in reproductive parameters of mice were a slight increase in gestation length. These changes were not considered to be biologically significant. HDDC had no effect on litter size, neonatal survival, sex ratio of pups, or pup morphology. Although there was no difference in birth weight compared to controls, there was a decrease in mean pup weight on Lactation Days 14 and 21 in the 160 mg/m^3 group. No other data regarding pup development after birth was provided.

4.1.2.3.2 Short et al. (1991)

Short et al. (1991) conducted a two-generation reproductive study and found dietary administration of up to 150 mg/kg/day of HMDA over two generations did not adversely affect reproduction or fertility in rats. Although this is an oral study, it indicates that HMDA is not a reproductive/developmental toxicant.

Rats received diets containing average daily doses of 0, 50, 150, and 500 mg/kg/day of HMDA over two generations. No treatment-related mortality was observed in any of the groups but the weight gain of adults and pups was slightly reduced in the high dose group. In the high dose group, the litter size was slightly reduced at birth. There was no adverse effect on survival during lactation in any of the treated groups. Thus, the dietary administration of up to 150 mg/kg/day of HMDA over two generations did not adversely affect reproduction or fertility in rats.

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

The MOA for irritation of the upper respiratory tract after chronic exposure is similar to the MOA for acute effects. Exposure concentration of the parent chemical will be used as the most appropriate dose metric. Please refer to Section 3.1.3 for details.

4.1.4 Point-of-Departure (POD) and Critical Effect

The LOAEL and NOAEL for the Hébert et al. (1993) study were 16 mg/m^3 HDDC (9.8 mg/m^3 HMDA) and 5 mg/m^3 HDDC (3.1 mg/m^3 HMDA). These were lower than the LOAEL and NOAEL from the Johannsen et al. (1987) study (51 mg/m^3 and 12.8 mg/m^3, respectively). Therefore, the LOAEL and NOAEL from the Hébert et al. (1993) study was chosen to use as the POD.

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.4) for the data in Tables 9-11 which were taken from the Hébert et al. (1993) study. Data were used to predict 95% lower confidence limits on the BMCs using dichotomous models. A default BMR of 10% was selected for extra risk (BMC10) and $BMCL_{10}$.

Hébert et al. (1993) observed degeneration of various regions of the nasal epithelium in both male and female rats and mice following exposure to HDDC. BMC modeling was conducted on the combined male and female data for each of the three histological endpoints that showed a dose response relationship and had at least two recorded incidences past the control value, making them suitable for BMC modeling. These histological endpoints include one lesion from the rat study; degeneration of the respiratory epithelium in the nasal passages. There were two lesions from the mouse study; hyaline degeneration of the respiratory epithelium and of the olfactory epithelium, both in the nasal passages. All of the available dichotomous models were run and the results can be found in Appendix 4. The best fit models for each of the histological end points are listed in Table 13 along with their detailed results.

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

Endpoint	Best Model	p value	AIC	Scaled Residual	BMC_{10}	$BMCL_{10}$
Rat Respiratory Epithelium Degeneration	Log Logistic	0.998	51.040	0.259	24.7291	15.1379
Mouse Hyaline Degeneration in Respiratory Epithelium	Multistage 3°	0.999	23.189	-0.35	18.1189	12.729
Mouse Hyaline Degeneration in Olfactory Epithelium	Multistage 2°	0.977	33.187	-0.452	11.3253	8.211

4.1.5 Dosimetric Adjustments

Dosimetric adjustments were made to each of the determined PODs (BMCLs).

4.1.5.1 Default Exposure Duration Adjustments

The effects of HDDC 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 x (D/24 h) x (F/7 d)

where:

D = Exposure duration, hours per day

F = Exposure frequency, days per week

Rat Respiratory Epithelium:

POD_{ADJ} = 15.1379 mg/m^3 x (6/24) x (5/7) = 2.7032 mg/m^3

Mouse Hyaline Degeneration in Respiratory Epithelium:

POD_{ADJ} = 12.729 mg/m^3 x (6/24) x (5/7) = 2.2730 mg/m^3

Mouse Hyaline Degeneration in Olfactory Epithelium:

POD_{ADJ} = 8.211 mg/m^3 x (6/24) x (5/7) = 1.4662 mg/m^3

4.1.5.2 Default Dosimetric Adjustments from Animal-to-Human Exposure

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

Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions considered. The mean mass median aerodynamic diameter (MMAD) for each chamber ranged from 1.62 – 1.72 µm with a geometric standard deviation (GSD) of 1.52 to 1.53 (Hébert et al. 1993). For the MPPD model, the high end was used for both parameters (MMAD = 1.72 µm; GSD = 1.53). The particle density for HDDC is not known, so a default value of 1 g/cm^3 was used. This is identical to the values used in the previous MPPD model in Section 3.1.5.2.

For the regional deposited dose ratio (RDDR) calculations, the TD used the default minute ventilation (VE) for humans (13,800 mL/min) given by USEPA (1994). Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and

breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TD used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model. The calculated human tidal volume is 842.74 ml/breath and the breathing frequency is 16.375 breaths per minute. Except for the parameter values discussed above, all remaining values used were default (refer to Appendix 1).

4.1.5.2.1 Rat Study

The minute volume was calculated based on the body weight for male (338 grams) and female rats (203 grams) observed in the study for exposure at 5 mg/m^3 (the BMCL). The average body weight was 270.50 grams and the calculated minute volume was 191.7728 mL/min (USEPA 1994).The chemical concentration is the POD_{ADJ} of 2.7032 mg/m^3. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). The head/extrathoracic surface areas for humans (200 cm^2) and rats (15 cm^2) were used as the normalizing factors were taken from the EPA RfC guidance (USEPA 1994). Once the deposition fractions for the rat ($DF_A = 0.5374$) and human ($DF_H = 0.4559$) were determined (Appendix 5), the regional deposited dose ratio (RDDR) was calculated as follows:

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

where: V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A = animal
H = human

$$RDDR = [191.7728 \text{ mL/min} / 13{,}800 \text{ mL/min}] \times [0.5374/0.4559] \times [200 \text{ cm}^2/15 \text{ cm}^2]$$

$$RDDR = 0.2184$$

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

POD_{HEC} for HDDC = POD_{ADJ} x RDDR = 2.7032 mg/m^3 x 0.2184 = 0.5904 mg/m^3
POD_{HEC} = 590.4 $\mu g/m^3$

4.1.5.2.2 Mouse Study

The final body weight of the mice at 5 mg/m^3 HDDC was 31.8 g for males and 26.8 g for females (Hébert et al. 1993). There were no consistent differences in the response between males

and females exposed to HDDC, so the average body weight of 29.3 g was used. The calculated minute volume was 34.0244 mL/min (USEPA 1994). The chemical concentration is the POD_{ADJ} for each endpoint examined. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). The head/extrathoracic surface areas for humans (200 cm^2) and mice (3 cm^2) used as the normalizing factors were taken from the EPA RfC guidance (USEPA 1994). Once the deposition fractions for the mouse (DF_A = 0.4936) and human (DF_H = 0.4559) were determined (Appendix 2), the RDDR was calculated as follows:

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

where: V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor (extrathoracic surface areas)
A = animal
H = human

$$RDDR = [34.0244 \text{ mL/min} / 13{,}800 \text{ mL/min}] \times [0.4936/0.4559] \times [200 \text{ cm}^2/3 \text{ cm}^2]$$

$$RDDR = 0.1780$$

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD (POD_{HEC}).

$$POD_{HEC} = POD_{ADJ} \times RDDR$$

Mouse Hyaline Degeneration in Respiratory Epithelium: 2.2730 mg/m^3 x 0.1780 = 0.4046 mg/m^3

$$POD_{HEC} = 404.6 \text{ } \mu g/m^3$$

Mouse Hyaline Degeneration in Olfactory Epithelium: 1.4662 mg/m^3 x 0.1780 = 0.2610 mg/m^3

$$POD_{HEC} = 261.0 \text{ } \mu g/m^3$$

4.1.5.3 Comparison of the Calculated Rat and Mouse POD_{HEC}

The following POD_{HEC} values were determined using the data from Hébert et al. (1993):

Rat Respiratory Epithelium: POD_{HEC} = 590.4 $\mu g/m^3$
Mouse Hyaline Degeneration in Respiratory Epithelium: POD_{HEC} = 404.6 $\mu g/m^3$
Mouse Hyaline Degeneration in Olfactory Epithelium: POD_{HEC} = 261.0 $\mu g/m^3$

4.1.6 Adjustment of POD_{HEC} by UFs

The lowest POD_{HEC} of 261.0 $\mu g/m^3$was based on hyaline degeneration in olfactory epithelium in

the mouse study by Hébert et al. (1993). 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 nonlinear MOA) in order to calculate a ReV. To calculate the chronic ReV, the POD_{HEC} was divided by appropriate UFs, for a total UF of 90:

- A UF_H of 10 was used to account for variation in sensitivity among the members of the human population. The TCEQ believes that a UF_H of 10 is sufficient to account for human variation including possible child/adult differences
- A UF_A of 3 was used because a default dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences
- A reduced UF_{Sub} of 3 was used because while some additional damage could accumulate and the response rate could be somewhat higher with a longer (i.e., chronic) exposure duration, the BMDL is considered unlikely to change by a factor greater than 3 (the UF_{Sub} value) since a factor of 3 difference in concentration (from 50 to 16 mg/m^3) is associated with a great reduction in response rate (from 90% to 15%) for the critical effect (Table 11). That is, the response rate from chronic exposure would have to increase to over 90% at 16 mg/m^3 for a UF_{Sub} of 3 to be insufficient to account for the difference between subchronic and chronic exposure. Additionally, while not deterministic, it is noted that applying the UF_{Sub} of 3 to the BMDL results in a concentration (2.7 mg/m^3) approximately half of the study NOAEL (5 mg/m^3) where 0% of the animals responded, which the TD views as adequately conservative. Finally, since HMDA has a low log K_{ow}, it would not be expected to bioaccumulate and cause a significantly different adverse effect after chronic exposure
- UF_D of 1 was used because the chronic database for HMDA is considered to be adequate. MOA information is available which indicates the adverse health effects observed in rodents are relevant for humans. Two subchronic studies were available: one in rats (Johannsen et al. 1987) and the other in rats and mice (Hébert et al. (1993). The differences between mice and rats were minimal (within a factor of two). Adequate studies indicate HMDA via inhalation is not a reproductive/developmental toxicant. The quality of the rat and mouse studies are high and the confidence in the chronic database is medium.

Chronic ReV= POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_D)
= 261.0 $\mu g/m^3$ / (10 x 3 x 3 x 1)
= 261.0 $\mu g/m^3$ / 90
= 2.9 $\mu g/m^3$

4.1.7 Conversion from HDDC to HMDA

In the key study, HDDC was used as the test chemical rather than HMDA. Therefore, the chronic ReV was initially calculated for HDDC and then adjusted for HMDA.

chronic ReV for HDDC = 2.9 µg/m^3

HDDC is 61.4% by weight HMDA (calculated from the molecular weight)

Therefore the chronic ReV of HMDA = 61.4/100 x 2.9 µg/m^3
= 1.7806 µg/m^3
= 1.8 µg/m^3 (rounded to 2 significant figures)

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 1.8 µg/m^3. The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target HQ of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 0.54 µg/m^3 (Table 14).

Table 14. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	**Summary**
Study	13 week bioassay (NTP 1993)
Study Population	F344/N rats and B6C3F1 mice, 10 males and 10 females/group
Study Quality	High
Exposure Method	Exposures via inhalation to HDDC aerosol at: 0, 1.6, 5, 16, 50, and 160 mg/m^3
Critical Effects	Hyaline degeneration of olfactory and respiratory epithelium in the nasal passages of mice
POD for observed adverse effect level (BMC_{10})	11.3253 mg/m^3 HDDC
POD (original animal study) ($BMCL_{10}$)	8.211 mg/m^3 HDDC
Exposure Duration	6 h/day, 5 d/wk for 13 wks
Extrapolation to continuous exposure (POD_{ADJ})	1.4662 mg/m^3 HDDC
POD_{HEC}	261.0 µg/m^3 HDDC
Total UFs	90
Intraspecies UF	10
Interspecies UF	3
LOAEL UF	Not applicable
Subchronic to chronic UF	3
Incomplete Database UF *Database Quality*	1 Medium to high
Chronic ReV (HQ = 1) HDDC	2.9 µg/m^3
Chronic ReV (HQ = 1) HMDA	**1.8 µg/m^3 (PM_{10})** [a]
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.54 µg/m^3 (PM_{10})**

[a] The derivation of the chronic ReV for HMDA has been published (Myers and Grant 2015).

4.2 Carcinogenic Potential

Chronic human or animal inhalation studies indicating that HMDA has carcinogenic potential via the inhalation route are not available, so an inhalation unit risk factor (URF) was not developed.

NTP (1993) states "1,6-Hexanediamine was not mutagenic in 4 strains of *Salmonella typhimurium*, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* tests were conducted with and without exogenous metabolic activation (S9). Negative results were also obtained in an *in vivo* test that measured the frequency of micronucleated erythrocytes in peripheral blood of male and female mice." According to USEPA (2005) guidelines, the cancer classification is "not likely to be carcinogenic to humans via inhalation exposure."

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 resulted in the derivation of the following values:

- Chronic ReV = 1.8 µg/m^3
- $^{chronic}ESL_{threshold(nc)}$= 0.54 µg/$m^3$

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 0.54 µg/m^3 (Table 2).

4.5 Chronic Observed Adverse Effect Level

The critical endpoint used in the chronic evaluation, hyaline degeneration in the olfactory epithelium in the nasal passages of mice (the most sensitive species), was also used as the basis for calculation of a chronic inhalation observed adverse effect level. The BMC_{10} value of 11.3253 mg/m^3 determined using data from the NTP 13-wk study (1993) was used as a POD (Table 8). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. No duration adjustment was made (TCEQ 2015a). However, an animal-to-human dosimetric adjustment was made to calculate a $LOAEL_{HEC}$:

For aerosols, the $LOAEL_{HEC}$ was calculated using the following equation:

$LOAEL_{HEC}$ = LOAEL x $RDDR_{ET}$ (Section 4.1.6.2.2)
= 11.3253 mg/m^3 x 0.1780
= 2.015 mg/m^3 HDDC
= 2.015 mg/m^3 HDDC x 61.4/100
(conversion from HDDC to HMDA, see section 4.1.7)
= 1.2 mg/m^3 HMDA (rounded to two significant figures)

The $LOAEL_{HEC}$ determined from animal studies, where effects occurred in some animals, represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 2.0 mg/m^3 is provided for informational purposes only (TCEQ 2015a).

The margin of exposure between the chronic inhalation observed adverse effect level of 1,200 $\mu g/m^3$ to the ReV of 1.8 $\mu g/m^3$ is a factor of 670.

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Appendix 1. Estimating Tidal Volume and Breathing Frequency Values for Input into the MPPD Model

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

Table 15. Human Tidal Volume and Breathing Frequency Data[a]

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

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

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

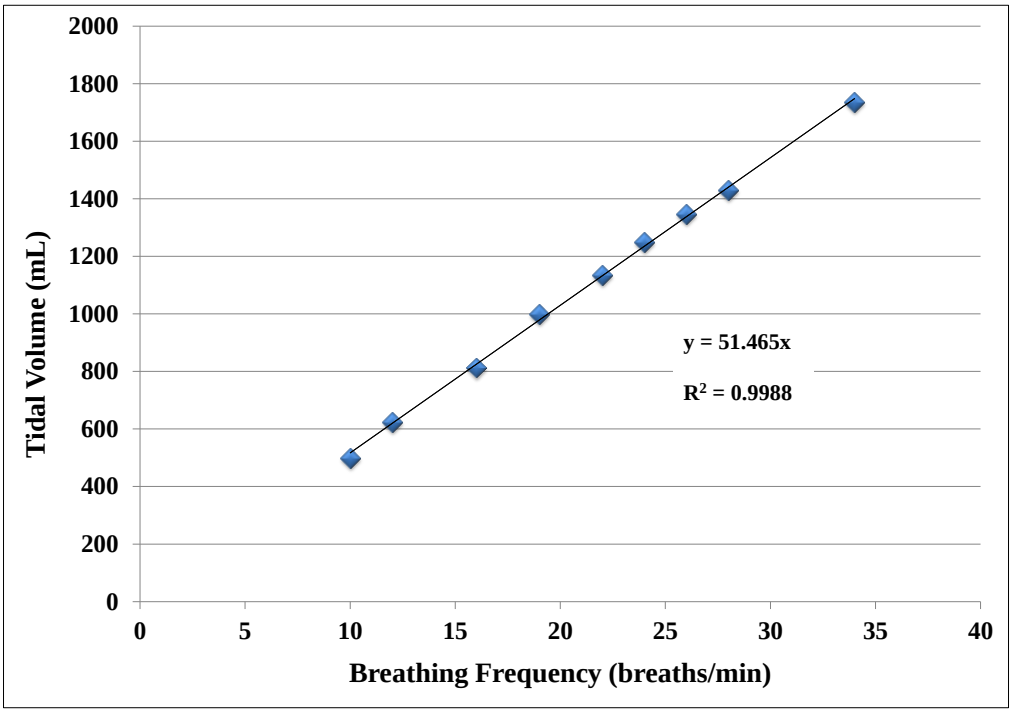

Figure 1. Relationship Between Human Tidal Volume and Breathing Frequency

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

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

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

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

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

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

(4) Tidal volume may then be calculated

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

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

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

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

= 117.4734 / 7.173911

= 16.375 breaths/min

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

= 51.465 * 16.375

= 842.74 mL/breath

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

Appendix 2. Acute Animal-to-Human Dosimetric Adjustments (MPPD Model)

In the key study, an aerosol of HDDC was used. The Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research and National Institute for Public Health and the Environment (RIVM) 2004 multiple path particle dosimetry model (MPPD) v 3.0 program (CIIT and RIVM 2004; Asgharian et al. 2014) was used to calculate the deposition fraction of HMDA in the target respiratory region. Parameters necessary for this program are particle diameter (MMAD = 1.72), particle density (GSD = 1.53), particle density (unknown, default value of 1 g/cm^3) and pulmonary regions considered. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). Once the total particle distribution was determined, the RDDR was calculated (Section 3.1.4.2).

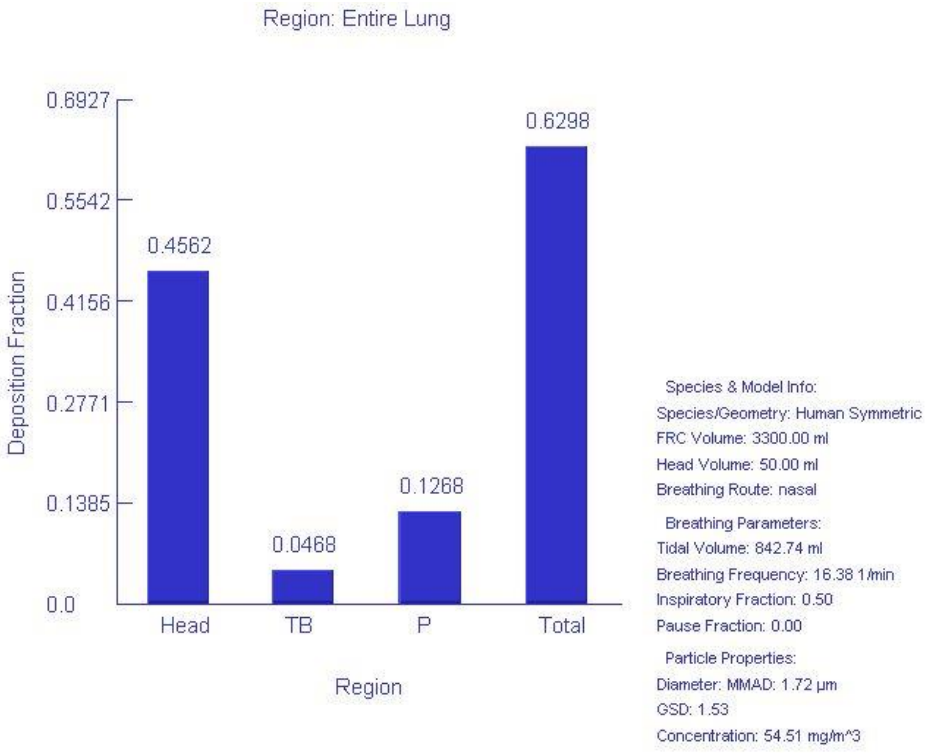

Figure 2. Human Output from the MPPD Model Used in the Acute Section

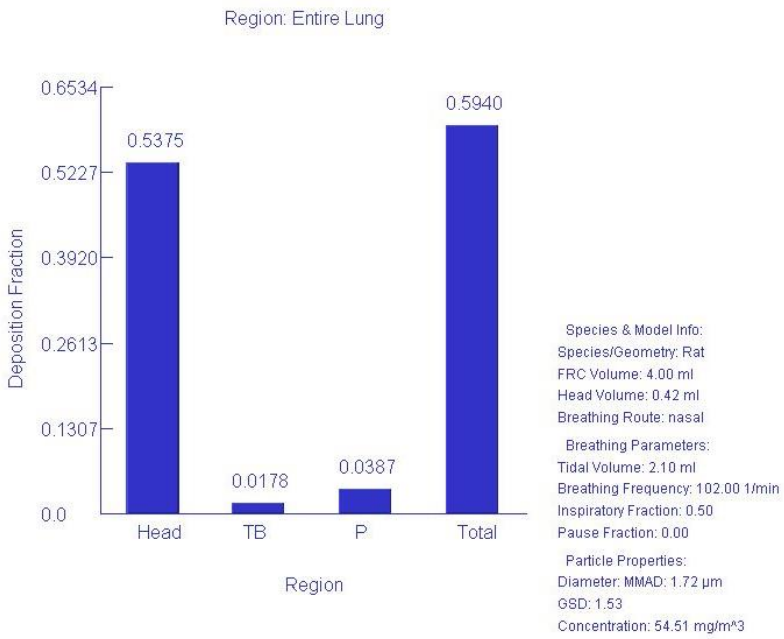

Figure 3. Rat Output from the MPPD Model Used in the Acute Section

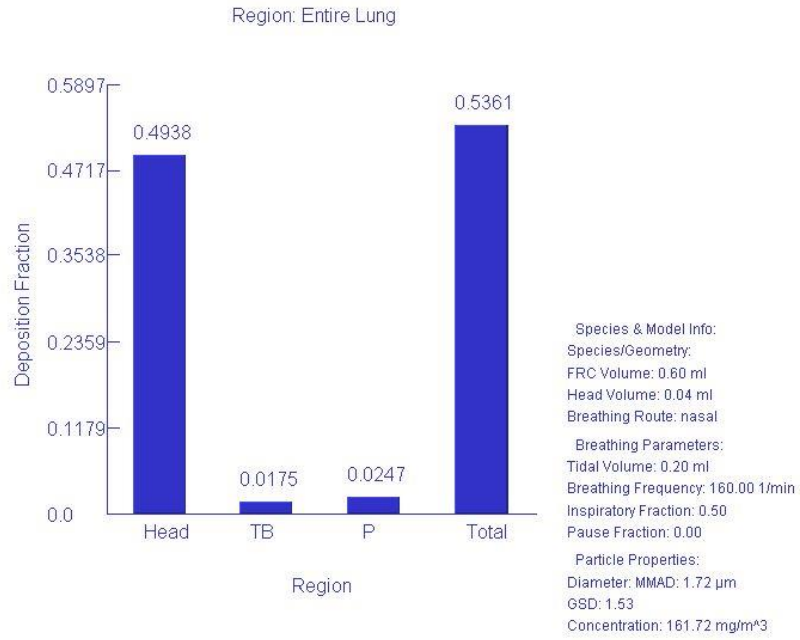

Figure 4. Mouse Output from the MPPD Model Used in the Acute Section

Appendix 3. Respiratory Tract Effects in Rats and Mice (Hébert et al. 1993)

Taken directly from Hébert et al. (1993). Concentrations are of HDDC, the dihydrochloride salt of HMDA

Rat Study

In rats in the 160 mg/m^3 exposure group, there was minimal to mild focal erosion/ulceration in the larynx as a result of necrosis of the laryngeal epithelium (Fig. 1 *of Hébert et al., 1993*). Associated with these erosions was a mild inflammatory infiltrate in the mucosa that sometimes extended into the lumen of the larynx. In two rats with laryngeal erosion/ulceration and inflammation there was also hyperplasia of the remaining laryngeal epithelium. In the nasal passages, chemical-related lesions were present in the olfactory and respiratory regions, primarily in Levels I and II (anterior and mid portion) of the nasal passages. Degeneration of the olfactory epithelium occurred only at the 160 mg/m^3 exposure level. The olfactory epithelium in the dorsal meatus of Level II was more commonly affected, but degeneration was also present on the ethmoid turbinates of Level III in some rats. Degeneration was characterized by focal areas of thinning of the olfactory epithelial layer (Fig. 2 *of Hébert et al., 1993*). This normally pseudostratified columnar epithelium was sometimes reduced to only one cell layer in thickness, and in some areas a respiratory or nonkeratinizing squamous epithelium replaced the olfactory epithelium. Frequently a vacuolar change in the olfactory epithelium was a part of the degenerative lesion, and in the more severely affected areas there was degeneration of the underlying olfactory nerve bundles (Fig. 3 *of Hébert et al., 1993*). Treatment-related lesions in the respiratory epithelium of the nasal passages included degeneration and focal erosion/ulceration of the mucosa in Levels I and II. Degeneration was characterized by loss of cilia and decreased height of the columnar epithelium; squamous metaplasia (nonkeratinizing) was present at the 160 mg/m^3 exposure level. In Levels I and II, the incidence of inflammation in the respiratory mucosa was increased slightly in the higher exposure groups, but the severity of the inflammation (minimal to mild) was not dose-related.

Mouse Study

In the larynx of mice, minimal to mild focal erosion/ulceration as a result of necrosis of the laryngeal epithelium was present at the 160 mg/m^3 exposure level. At the margins of some erosions, there was focal necrosis or hyperplasia of the adjacent epithelium. In the nasal passages, exposure-related lesions were present in the respiratory and olfactory regions, primarily in the midportion (Levels II and III). In the respiratory epithelium, the primary change was hyaline degeneration characterized by the accumulation of an eosinophilic proteinaceous material in the cytoplasm. Minimal to mild focal areas of erosion/ulceration and inflammation were present at the highest exposure level (Fig. 4 *of Hébert et al., 1993*). Hyaline degeneration of the olfactory epithelium was generally limited to the 50 and 160 mg/m^3 exposure levels. This

degeneration was characterized by the accumulation of eosinophilic proteinaceous material in the olfactory sustentacular cells, with a resultant loss of olfactory sensory cells (Figs. 5 and 6 *of Hébert et al., 1993*).

Appendix 4. Benchmark Concentration (BMC) Modeling

A total of three histological endpoints in both the rat and mouse studies from Hébert et al. (1993) were found suitable for benchmark concentration model (i.e. effect showed a dose-response relationship, at least two response points above control). The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.5). Data were used to predict 95% lower confidence limits on the BMCs using dichotomous models. A default BMR of 10% was selected for extra risk (BMC10) and BMCL10. All of the models for each histological endpoint are presented below, with the best fit model in bold and shown graphically below its respective table.

BMDS Summary: Rat study – Degeneration of Respiratory Epithelium in the Nose/Nasal Passages (total of 20 rats, 10 males and 10 females, per dose group)

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Rats (male and female)	0	0	0	1	7	18

Table 16. Model Predictions for Degeneration of Respiratory Epithelium in Rats

Model[a]	**Goodness of fit**		**BMD_{10Pct}**	**$BMDL_{10Pct}$**	**Basis for model selection**
	***p*-value**	**AIC**			
Gamma	0.997	51.096	23.6	13.7	Of the models that provided an adequate fit and a valid BMDL estimate, the <model name> model was selected based on lowest AIC.
Logistic	0.173	58.625	38.1	27.9	
LogLogistic	**0.998**	**51.040**	**24.7**	**15.1**	
Probit	0.239	57.390	36.7	27.5	
LogProbit	0.995	51.063	23.5	14.7	
Weibull	0.982	51.459	22.9	13.1	
Multistage 5°[b]	0.914	52.152	23.9	11.6	
Multistage 4°[c]	0.914	52.152	23.9	11.6	
Multistage 3°	0.914	52.152	23.9	11.7	
Multistage 2°	0.914	52.152	23.9	11.9	
Quantal-Linear	0.504	55.111	10.7	7.71	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1.6, 5, 16, 50, and 160 were 0.000, -0.062, -0.233, 0.259, -0.124, and 0.073, respectively.
[b] The Multistage 5° model may appear equivalent to the Multistage 4° model, however differences exist in digits not displayed in the table.
[c] The Multistage 4° model may appear equivalent to the Multistage 5° model, however differences exist in digits not displayed in the table.

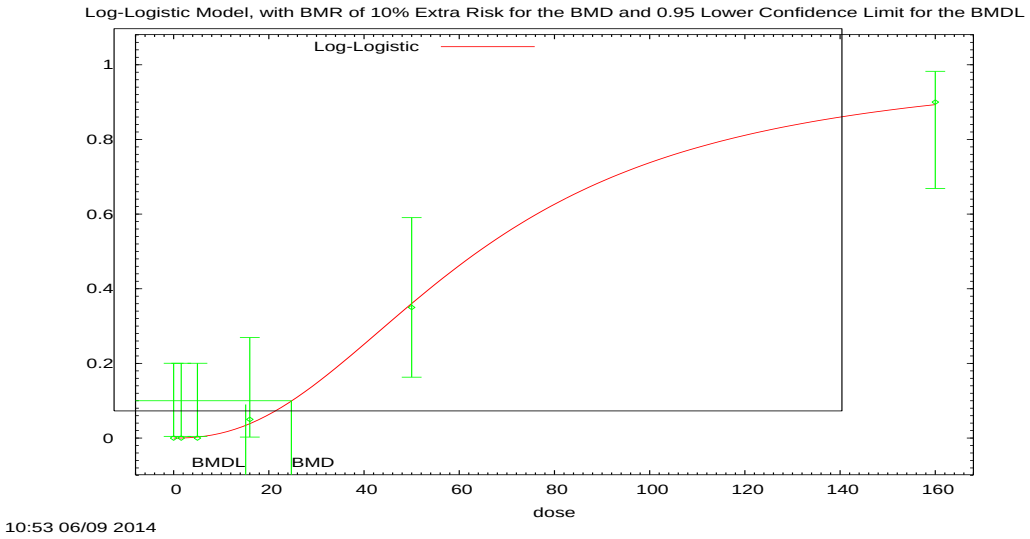

Figure 5. Incidence Rate by Concentration (mg/m^3) for Degeneration of Respiratory Epithelium in Rat Nose/Nasal Passages

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

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]
Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk
BMD = 24.7291
BMDL at the 95% confidence level = 15.1379

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-9.6532E+00	-5.3467E+00
slope	2.32419	1.29631

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-23.4209	6			
Fitted model	-23.52	2	0.198221	4	0.9954
Reduced model	-62.7188	1	78.5958	5	<.0001

AIC: = 51.04

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	20	0
1.6	0.0002	0.004	0	20	-0.062
5	0.0027	0.054	0	20	-0.233
16	0.0388	0.776	1	20	0.259
50	0.3633	7.267	7	20	-0.124
160	0.895	17.899	18	20	0.073

Chi^2 = 0.15

d.f = 4

p-value = 0.9975

BMDS Summary: Mouse study – Hyaline Degeneration of Respiratory Epithelium in the Nose/Nasal Passages (total of 20 mice, 10 males and 10 females, per dose group)

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Mice (male and female)	0	0	0	1	18	20

Table 17. Model Predictions for Hyaline Degeneration of Respiratory Epithelium in Mice

Model[a]	**Goodness of fit**		**BMD_{10Pct}**	**$BMDL_{10Pct}$**	**Basis for model selection**
	***p*-value**	**AIC**			
Gamma	1.000	24.947	18.9	13.2	Of the models that provided an adequate fit and a valid BMDL estimate, the <model name> model was selected based on lowest AIC.
Logistic	0.983	25.547	23.1	16.3	
LogLogistic	1.000	24.977	19.0	13.5	
Probit	0.997	25.194	21.2	15.2	
LogProbit	1.000	24.944	18.4	13.5	
Weibull	1.000	24.985	20.0	13.0	
Multistage 5°	0.999	26.998	20.2	12.9	
Multistage 4°	1.000	24.997	20.2	12.9	
Multistage 3°	**0.999**	**23.189**	**18.1**	**12.7**	
Multistage 2°	0.696	27.064	12.2	9.44	
Quantal-Linear	0.0139	43.740	4.58	3.30	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1.6, 5, 16, 50, and 160 were 0.000, -0.038, -0.211, -0.350, 0.133, and 0.000, respectively.

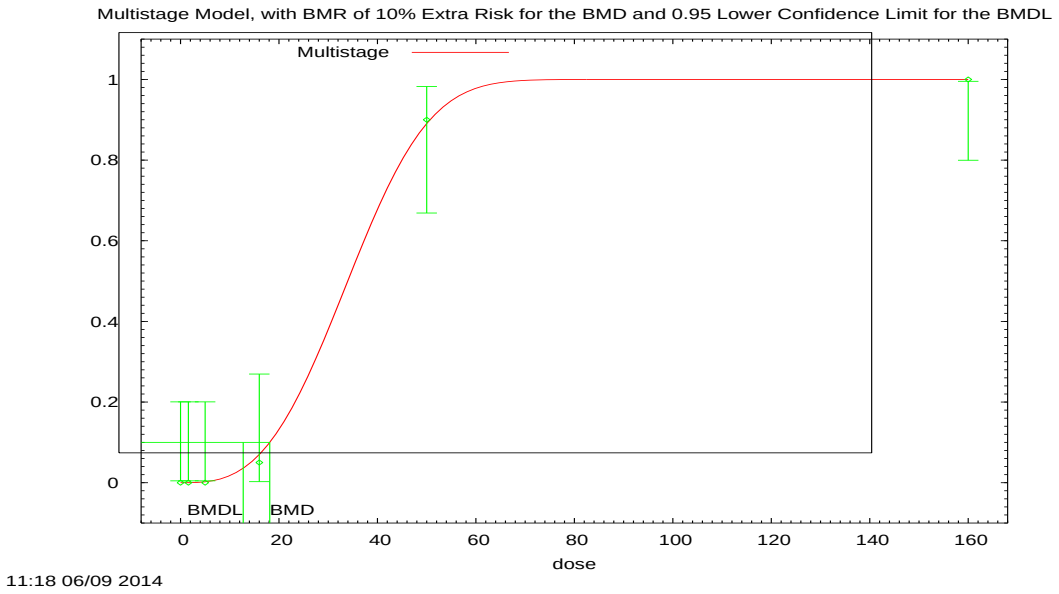

Figure 6. Incidence Rate by Concentration (mg/m^3) for Hyaline Degeneration of Respiratory Epithelium in Mice

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

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

Benchmark Dose Computation.

BMR = 10% Extra risk
BMD = 18.1189
BMDL at the 95% confidence level = 12.729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.0000177126	2.4547E+13

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-10.472	6			
Fitted model	-10.5944	1	0.244892	5	0.9986
Reduced model	-75.6697	1	130.396	5	<.0001

AIC: = 23.1888

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	20	0
1.6	0.0001	0.001	0	20	-0.038
5	0.0022	0.044	0	20	-0.211
16	0.07	1.4	1	20	-0.35
50	0.8907	17.815	18	20	0.133
160	1	20	20	20	0

Chi^2 = 0.19

d.f = 5

p-value = 0.999

BMDS Summary: Mouse study – Hyaline Degeneration of Olfactory Epithelium in the Nose/Nasal Passages (total of 20 mice, 10 males and 10 females, per dose group)

Dose HDDC	0 mg/m^3	1.6 mg/m^3	5.0 mg/m^3	16 mg/m^3	50 mg/m^3	160 mg/m^3
Mice (male and female)	0	0	0	3	18	20

Table 18. Model predictions for Hyaline Degeneration of Olfactory Epithelium in mice

Model[a]	**Goodness of fit**		**BMD_{10Pct}**	**$BMDL_{10Pct}$**	**Basis for model selection**
	***p*-value**	**AIC**			
Gamma	1.000	34.031	14.1	9.28	Of the models that provided an adequate fit and a valid BMDL estimate, the <model name> model was selected based on lowest AIC.
Logistic	0.755	36.541	17.7	12.6	
LogLogistic	0.999	34.102	14.3	9.97	
Probit	0.867	35.657	16.6	12.0	
LogProbit	1.000	33.930	14.2	9.90	
Weibull	0.994	34.312	14.1	8.88	
Multistage 5°	0.990	34.438	14.1	8.74	
Multistage 4°	0.990	34.438	14.1	8.80	
Multistage 3°	0.990	34.438	14.1	8.88	
Multistage 2°	**0.977**	**33.187**	**11.3**	**8.21**	
Quantal-Linear	0.0706	46.745	4.15	3.00	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1.6, 5, 16, 50, and 160 were 0.000, -0.205, -0.644, -0.452, 0.378, and 0.000, respectively.

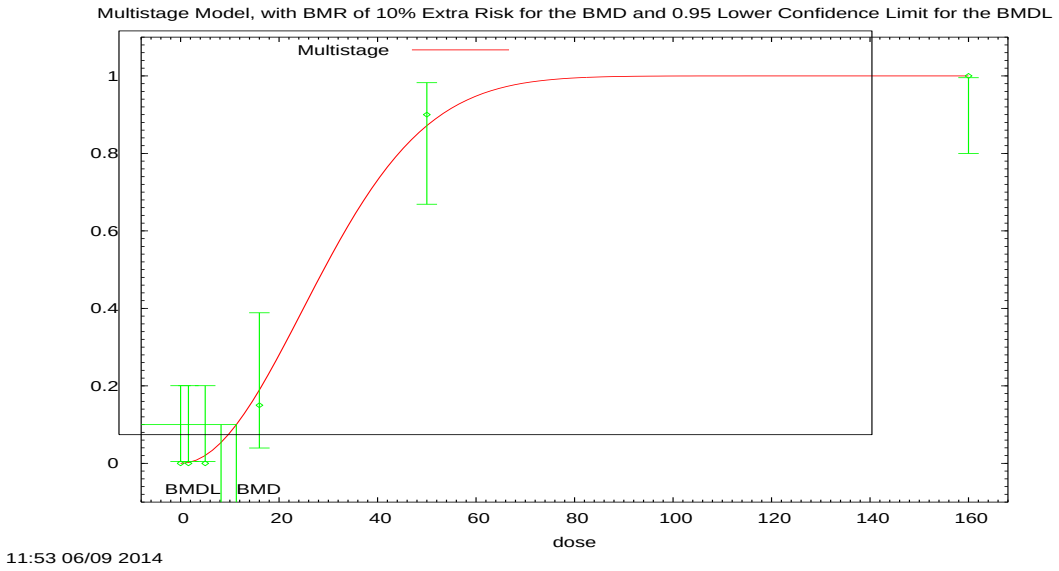

Figure 7. Incidence Rate by Concentration (mg/m^3) for Hyaline Degeneration of Olfactory Epithelium in the Mouse Nose/Nasal Passages

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

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

Benchmark Dose Computation.

BMR = 10% Extra risk
BMD = 11.3253
BMDL at the 95% confidence level = 8.21101

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.000821446	3.9570E+15

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-14.9558	6			
Fitted model	-15.5936	1	1.27556	5	0.9374
Reduced model	-77.0562	1	124.201	5	<.0001

AIC: = 33.1872

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	20	0
1.6	0.0021	0.042	0	20	-0.205
5	0.0203	0.407	0	20	-0.644
16	0.1897	3.793	3	20	-0.452
50	0.8717	17.435	18	20	0.378
160	1	20	20	20	0

Chi^2 = 0.8

d.f = 5

p-value = 0.9767

Appendix 5. Chronic Animal-to-Human Dosimetric Adjustments (MPPD Model)

Rat Study

In the key study, an aerosol of HDDC was used. The Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research and National Institute for Public Health and the Environment (RIVM) 2004 multiple path particle dosimetry model (MPPD) v 3.0 program (CIIT and RIVM 2004) was used to calculate the deposition fraction of HMDA in the target respiratory region. Parameters necessary for this program are particle diameter (MMAD = 1.72), particle density (GSD = 1.53), particle density (unknown, default value of 1 g/cm^3) and pulmonary regions considered. The target region for HDDC was considered to be the total particle distribution in the larynx and nasal cavity (head region). Once the total particle distribution was determined, the RDDR was calculated (Section 4.1.5.2).

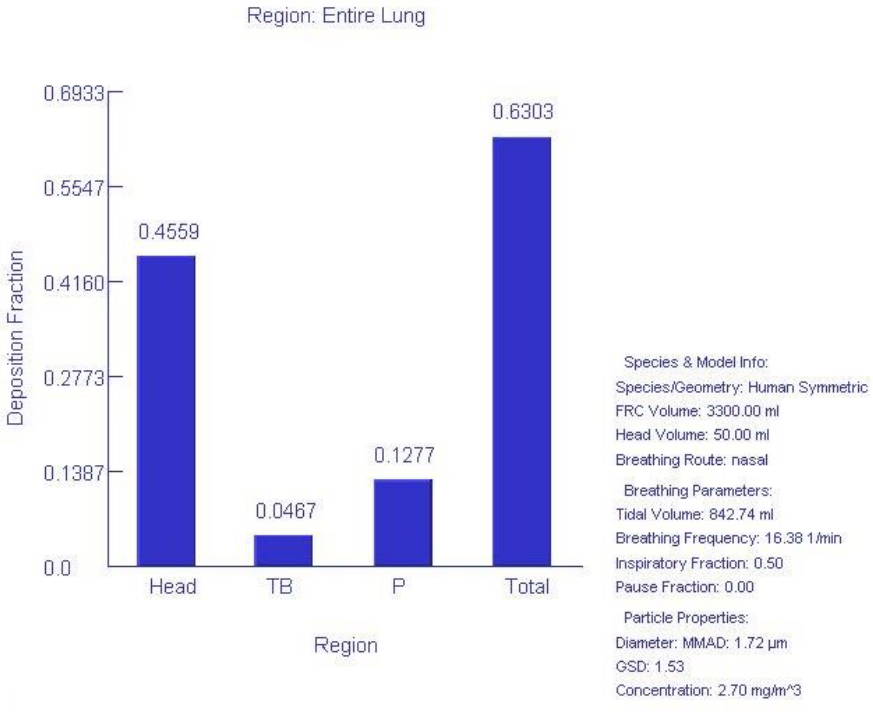

Figure 8. Human Output from the MPPD Model used in the Chronic Section

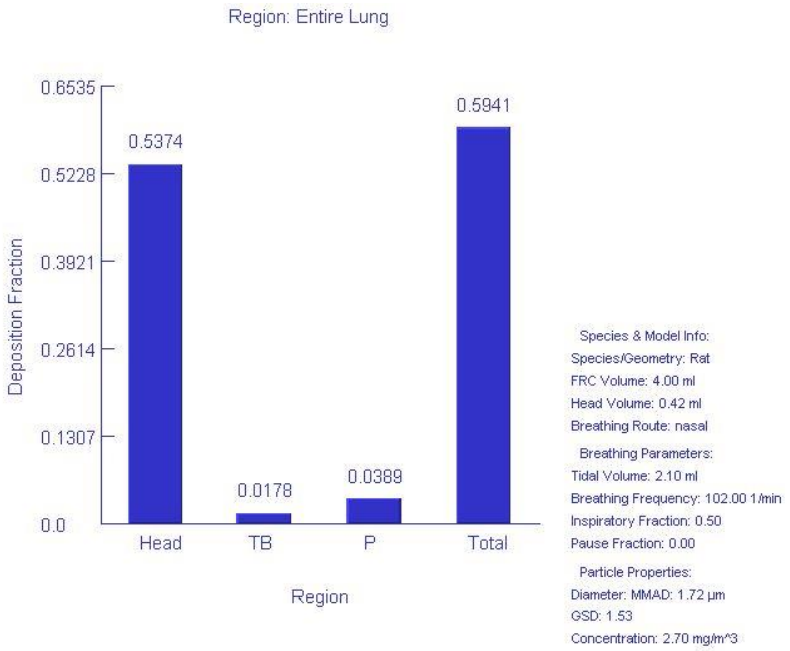

Figure 9. Rat Output from the MPPD Model Used in the Chronic Section

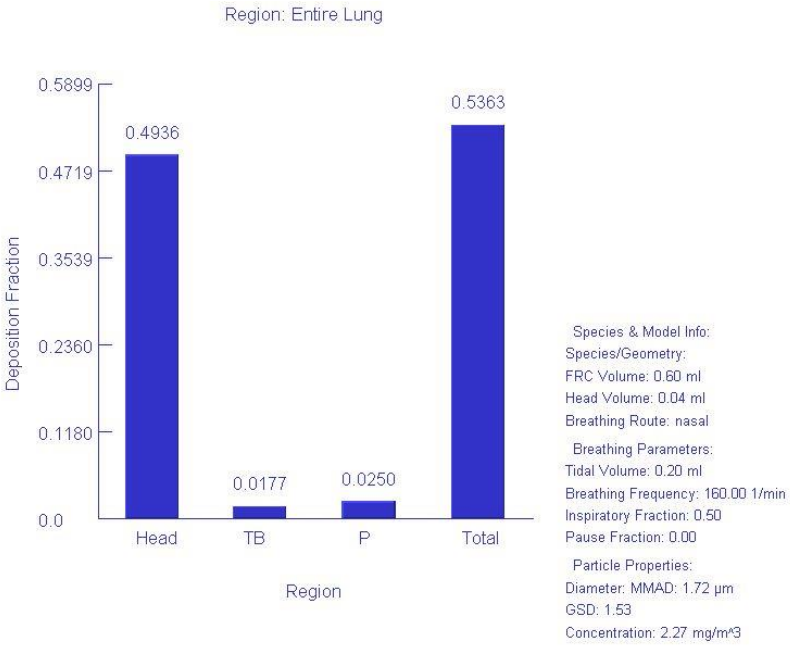

Figure 10. Mouse Output from the MPPD Model Used in the Chronic Section