# 4,4-Methylene Diphenyl Diisocyanate (MDI), All Isomers

**CAS Registry Number 101-68-8**

# 1,6-Hexamethylene Diisocyanate (HDI), All Isomers

**CAS Registry Number 822-06-0**

Prepared by
Toxicology, Risk Assessment, and Research Division

**Development Support Document**

**Final, December 9, 2019**

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

# DSD History

| Effective Date | Reason |
|---|---|
| December 30, 2016 | MDI DSD proposed for public comment |
| January, 2017 | MDI DSD retracted to allow for submission of public toxicity information |
| March 10, 2017 | Public request for toxicity information for MDI and HDI |
| March 6, 2019 | Combined MDI and HDI DSD proposed for public comment |
| December 9, 2019 | MDI and HDI DSD posted as final |

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# Acronyms and Abbreviations

| Acronyms and Abbreviations | Definition |
|---|---|
| AM | alveolar macrophage |
| AMCV | air monitoring comparison value |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| $^{o}C$ | degrees Celsius |
| CNS | central nervous system |
| d | day(s) |
| DSD | development support document |
| ESL | effects screening level |
| $^{acute}ESL$ | acute health-based effects screening level for chemicals 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 |
| GSD | geometric standard deviation ($\sigma_g$) |
| h | hour(s) |
| $(H_{b/g})_A$ | blood:gas partition coefficient, animal |
| mm Hg | millimeters of mercury |
| HEC | human equivalent concentration |
| HDI | 1,6-Hexamethylene Diisocyanate |

| Acronyms and Abbreviations | Definition |
|---|---|
| HQ | hazard quotient |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IOAEL | Inhalation Observed Adverse Effect Level |
| $^{acute}$IOAEL | acute inhalation observed adverse effect level |
| $^{subacute}$IOAEL | subacute inhalation observed adverse effect level |
| $^{chronic}$IOAEL$_{(nc)}$ | chronic inhalation observed adverse effect level (noncancer effects) |
| $^{chronic}$IOAEL$_{(c)}$ | chronic inhalation observed adverse effect level (cancer effects) |
| kg | kilogram |
| LOAEL | lowest-observed-adverse-effect-level |
| LOEL | lowest-observed-effect-level |
| MDI | Methylene Diphenyl Diisocyanate |
| 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 | mass median aerodynamic diameter |
| MOA | mode of action |
| MRL | minimal risk level |
| MW | molecular weight |
| NOAEL | no-observed-adverse-effect-level |
| NOEL | no-observed-effect-level |
| OECD | Organization for Economic Cooperation and Development |
| PM | particulate matter |
| POD | point of departure |

| Acronyms and Abbreviations | Definition |
|---|---|
| $POD_{ADJ}$ | point of departure adjusted for exposure duration |
| $POD_{HEC}$ | point of departure adjusted for human equivalent concentration |
| ppb | parts per billion |
| POE | portal-of-entry |
| ppm | parts per million |
| ReV | reference value |
| Acute ReV | acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements |
| Acute ReV-24hr | acute 24-hour health-based reference value for chemicals meeting minimum database requirements |
| Chronic $ReV_{threshold(nc)}$ | chronic health-based reference value for threshold dose response noncancer effects |
| RDDR | regional deposition dose ratio |
| RfC | reference concentration |
| RGDR | regional gas dose ratio |
| SD | Sprague-Dawley rats |
| TCEQ | Texas Commission on Environmental Quality |
| TRARD | Toxicology, Risk Assessment, and Research 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 |
| wk | Week(s) |

# Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation, respectively, of 4,4-Methylene Diphenyl Diisocyanate (MDI) and 1,6-Hexamethylene Diisocyanate (HDI) in the aerosol/particulate matter (PM) phase for use in air permitting and air monitoring. Table 3 and Table 4 provide a summary of health- and welfare-based values from an acute and chronic evaluation, respectively, of MDI and HDI in the vapor phase. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015a) for an explanation of reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 5 and Table 6 provide summary information on physical/chemical data for MDI and HDI monomers and homopolymers (polyisocyanates). Table 7 lists five isomers and polymers of MDI including 4,4'-MDI, 2,4'-MDI, 2,2'-MDI, non-isomer-specific MDI, and PMDI; and HDI monomer and homopolymer.

**Table 1. Acute Health and Welfare-Based Screening Values for MDI and HDI, All Isomers, Aerosol**

| Screening Level Type | Duration | Value 1 (µg/m³) | Value 2 (ppb) | Usage | Flags | Surrogated / RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Acute ReV | 1 h | 27 | -- | N | none | -- | Mild acute pulmonary irritation (e.g., decreased tidal volume) | Aerosol, treat as PM. |
| Acute ReV-24hr | -- | -- | -- | -- | -- | -- | -- | -- |
| **$^{acute}$ESL [a]** | **1 h** | **8.1** | **--** | **P** | **S,D** | **--** | **Same as above.** | **Same as above.** |
| $^{acute}$IOAEL | 6 h | 1,600 | -- | N | none | -- | Same as above. | Same as above. |
| $^{subacute}$IOAEL | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{acute}ESL_{odor}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{acute}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |

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

[a] Based on the acute 1-h ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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

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

**Table 2. Chronic Health and Welfare-Based Screening Values for MDI and HDI, All Isomers, Aerosol**

| Screening Level Type | Duration | Value 1 (µg/m³) | Value 2 (ppb) | Usage | Flags | Surrogated/ RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Chronic $ReV_{threshold(nc)}$ | 70 yr | 1.8 | -- | N | none | -- | Increases in lung weights, alveolar macrophage (AM) influx, focal interstitial fibrosis with round-cell infiltrations, and bronchoalveolar proliferations in rats. | Aerosol, treat as PM. |
| **$^{chronic}ESL_{threshold(nc)}$ [a]** | **70 yr** | **0.55** | **--** | **P** | **S,D** | **--** | **Same as above.** | **Same as above.** |
| $^{chronic}IOAEL_{(nc)}$ | 70 yr | 760 | -- | N | -- | -- | Same as above | Same as above. |
| $^{chronic}ESL_{threshold(c)}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{chronic}ESL_{nonthreshold(c)}$ | **--** | **--** | **--** | **--** | **--** | **--** | **--** | Data are inadequate for an assessment of human carcinogenic potential. |
| $^{chronic}IOAEL_{(c)}$ | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{chronic}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{chronic}ESL_{animal}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |

Bold values used for air permit reviews.

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

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

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

**Table 3. Acute Health and Welfare-Based Screening Values for MDI and HDI, All Isomers, Vapor**

| Screening Level Type | Duration | Value 1 (µg/m$^3$) | Value 2 (ppb) | Usage | Flags | Surrogated / RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Acute ReV | 1 h | 11 | -- | N | none | -- | Degenerative changes of olfactory epithelium in rats. | Vapor phase. |
| Acute ReV-24hr | -- | -- | -- | -- | -- | -- | -- | -- |
| **$^{acute}$ESL [a]** | **1 h** | **3.3** | **--** | **P** | **S,D** | **--** | **Same as above.** | **Same as above.** |
| $^{acute}$IOAEL | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{subacute}$IOAEL | 5 d | 690 | -- | N | none | -- | Same as above. | Same as above. |
| $^{acute}ESL_{odor}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{acute}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |

Bold values used for air permit reviews; HDI is not monitored for by the TCEQ's ambient monitoring program.

[a] Based on the acute 1-h ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

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

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

**Table 4. Chronic Health and Welfare-Based Screening Values for MDI and HDI, All Isomers, Vapor**

| Screening Level Type | Duration | Value 1 (µg/m³) | Value 2 (ppb) | Usage | Flags | Surrogated/ RPF | Critical Effect(s) | Notes |
|---|---|---|---|---|---|---|---|---|
| Chronic $ReV_{threshold(nc)}$ | 70 yr | 0.21 | -- | N | none | -- | Olfactory epithelial degeneration in rats. | Vapor phase. |
| **$^{chronic}ESL_{threshold(nc)}$ [a]** | **70 yr** | **0.063** | **--** | **P** | **S,D** | **--** | **Same as above.** | **Same as above.** |
| $^{chronic}IOAEL_{(nc)}$ | 2 yr | 170 | -- | N | none | -- | Same as above. | Same as above. |
| $^{chronic}ESL_{threshold(c)}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{chronic}ESL_{nonthreshold(c)}$ | **--** | **--** | **--** | **--** | **--** | **--** | **--** | Data are inadequate for an assessment of human carcinogenic potential. |
| $^{chronic}IOAEL_{(c)}$ | -- | -- | -- | -- | -- | -- | -- | -- |
| $^{chronic}ESL_{veg}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |
| $^{chronic}ESL_{animal}$ | -- | -- | -- | -- | -- | -- | -- | No data found. |

Bold values used for air permit reviews.

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

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

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

**Table 5. Chemical and Physical Data for MDI Monomer and Polymeric MDI (PMDI)**

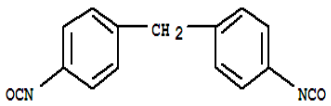
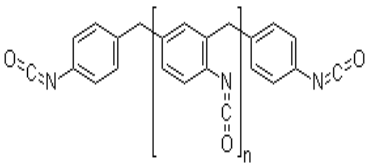
| Parameter | MDI | PMDI | Reference |
|---|---|---|---|
| Molecular Formula | $C_{15}H_{10}N_2O_2$ | $[C_6H_3(NCO)CH_2]n$ | HSDB 2018a,b |
| Chemical Structure |  |  | IPCS 2000 |
| Molecular Weight | 250.252 | Not applicable | HSDB 2018a,b |
| Physical State | Fused solids, flakes, crystals | Viscous liquid | HSDB 2018a,b |
| Color | White to yellow | Dark amber | HSDB 2018a,b |
| Odor | Odorless | -- | HSDB 2018a,b |
| CAS Registry Number | 101-68-8 | 9016-87-9 | HSDB 2018a,b |
| Synonyms | Diphenylmethane diisocyanate, Methylene bisphenyl isocyanate, 4,4'-Methylenediphenyl diisocyanate, Non-isomeric-specific MDI | Polyphenyl polymethylene polyisocyante | NIOSH 2007; HSDB 2018b |
| Solubility in water, mg/L | 1.51 mg/L at 25°C | --- | HSDB 2018a |
| Log $P_{ow}$ or $K_{ow}$ | 5.22 | --- | HSDB 2018a |
| Vapor Pressure | 5.1 x $10^{-6}$ mm Hg at 25°C | < $10^{-4}$ mm Hg at 25°C | HSDB 2018a,b |
| Density | 1.23 at 25°C | 1.23 at 25°C | HSDB 2018a,b |
| Melting Point | 37°C | 38°C | HSDB 2018a,b |
| Boiling Point | 196°C | 196°C | HSDB 2018a,b |
| Conversion Factors | 1 µg/$m^3$ = 0.098 ppb<br>1 ppb = 10.24 µg/$m^3$ | Not applicable | Toxicology Division |

**Table 6. Chemical and Physical Data for HDI Monomer and Polyisocyanate**

| Parameter | HDI | HDI Polyisocyanate | Reference |
|---|---|---|---|
| Molecular Formula | $C_{15}H_{22}N_2O_2$ | $(C_8H_{12}N_2O_2)n$ | ACGIH 2001 |
| Chemical Structure |  | | ChemBook |
| Molecular Weight | 168.2 | 504-2185 | ACGIH 2001 ECHA 2015 |
| Physical State | Liquid | Liquid | ACGIH 2001 ECHA 2015 |
| Color | Clear and colorless | Colorless to pale yellow | ACGIH 2001 ECHA 2015 |
| Odor | Sharp, pungent | Odorless | ACGIH 2001 ECHA 2015 |
| CAS Registry Number | 822-06-0 | 28182-81-2 | ACGIH 2001 ECHA 2015 |
| Synonyms | 1,6-Hexamethylene diisocyanate; HDI; 1,6-Diisocyanatohexane | Poly(hexamethylene diisocyanate); HDI homopolymer | ACGIH 2001; ECHA 2015 |
| Solubility in water, mg/L | Reacts with water | Reacts with water | ACGIH 2001 ECHA 2015 |
| Log $P_{ow}$ or $K_{ow}$ | 3.20 | 4.28 to 24.25 | HSDB 2016; ECHA 2015 |
| Vapor Pressure | 0.05 mm Hg at 25°C | < 0.001 mm Hg at 20°C | NIOSH 2016; ECHA 2015 |
| Density | 1.04 at 25°C | 1.16 at 25°C | ACGIH 2001; ECHA 2015 |
| Melting Point | -67°C | Between -51.3 and -28.4 °C | NIOSH 2016 ECHA 2015 |
| Boiling Point | 212.8°C | 418°C | ACGIH 2001 ECHA 2015 |
| Conversion Factors | 1 µg/m$^3$ = 0.15 ppb<br>1 ppb = 6.88 µg/m$^3$ | Not applicable | Toxicology Division |

**Table 7. MDI and HDI Isomers and CAS Numbers.**

| Substance | CAS Number |
|---|---|
| 2,2-Methylene Diphenyl Diisocyanate (2,2-MDI) | 2536-05-2 |
| 2,4-Methylene Diphenyl Diisocyanate (2,4-MDI) | 5873-54-1 |
| 4,4-Methylene Diphenyl Diisocyanate (4,4-MDI) | 101-68-8 |
| Non-isomeric Specific MDI (MDI) | 26447-40-5 |
| Polymethylene polyphenyl isocyanate (PMDI) | 9016-87-9 |
| 1,6-Hexamethylene Diisocyanate (HDI) | 822-06-0 |
| Hexamethylene Diisocyanate Homopolymer | 28182-81-2 |

# Chapter 2 Background Information

## *2.1 Physical/Chemical Properties*

### 2.1.1 MDI

MDI is a solid at room temperature (25°C), and PMDI is a viscous liquid at room temperature. The vapor pressure (VP) for both MDI and PMDI is $< 10^{-4}$ mm Hg at 25°C, and the melting point (MP) is 37-38°C. MDI vapor is only released when MDI is heated (e.g. 80-120°C). The physical/chemical properties for MDI and PMDI are listed in Table 5.

### 2.1.2 HDI

HDI monomer is a clear, colorless to light-yellow liquid with a sharp, irritating odor. The main chemical and physical properties of HDI monomer and polyisocyanate are summarized in Table 6.

## *2.2 Major Uses or Sources*

### 2.2.1 MDI

MDI usually occurs as a mixture of several isomers and oligomers: one common mixture is approximately 40-50% 4,4'-MDI, 2.5-4.0% 2,4'-MDI, 0.1-0.2% 2,2'-MDI, and the remaining is oligomers. 4,4'-MDI is the most commercially common isomer and is referred to as pure MDI (ATSDR 2018). PMDI is commonly called polymeric, generic, or non-isomer-specific MDI. PMDI, a dark amber viscous liquid, is a mixture that contains 25-80% monomeric 4,4'-MDI as well as oligomers containing 3-6 rings and other minor isomers, such as the 2,2'-isomer (IPCS 2000). It

is used as a binder resin for particle board and as a foundry core binder resin (IARC 1999, HSDB 2018a). MDI is highly reactive in the environment or when taken up by organisms and is rapidly hydrolyzed to form 4,4'-methylenedianiline (MDA), which reacts with excess MDI to yield insoluble oligoureas and polyureas (IPCS 2000). MDI is used for polyurethane elastomers (rollers, packing, rubber vibration insulators, synthetic leather, etc.), spandex fiber, and rubber shoe soles. PMDI is used to make rigid and flexible foam, foundry resins and binders, and self-healing insulating material (IPCS 2000). MDI vapor, or more commonly aerosol (PM), can be released into the atmosphere from sites of industrial manufacture and use. MDI vapor is only released when MDI is heated (e.g., 80-120°C). Potential exposures to both vapor and aerosol MDI are associated with the production, handling, use, and disposal of MDI and MDI-containing products and material (IARC 1999, ATSDR 2018). Neither MDI nor PMDI are monitored by the TCEQ's ambient air monitoring program.

### 2.2.2 HDI

HDI is used as a polymerizing agent in polyurethane paints and coatings. HDI is not used as the monomer but is industrially processed to higher molecular weight compounds (polymeric forms). The higher molecular weight HDI compounds (HDI biuret (HDI-BT) or HDI isocyanurate (HDI-IC)) are used in industrial applications (mainly surface coatings) with excellent lightfastness and weather stability. Industry often refers to HDI-BT and HDI-IC jointly as HDI polyisocyanates. Monomeric HDI vaporizes readily. It can be released into the environment during manufacturing or processing of HDI or during spray applications of polymer paints containing residual amounts of monomer HDI (OECD 2001). HDI polyisocyanates form oily droplets in water and hydrolyze rapidly to form hexamethylene diamine (HDA) and polyurea. Neither HDI nor HDI polyisocyanate are monitored by the TCEQ's ambient air monitoring program.

# Chapter 3 Acute Evaluation

## *3.1 Health-Based Acute ReV and ESL for MDI and HDI, Aerosol*

Exposure to MDI and HDI aerosols primarily causes adverse effects on the respiratory system in both animals and humans. Acute exposure to very high concentrations of MDI or HDI in humans can cause pulmonary edema, coughing, and shortness of breath. The most common health endpoints caused by inhalation of MDI or HDI aerosols are occupationally-induced asthma, hypersensitivity pneumonitis, decreases in lung function, and inflammation of the upper respiratory tract. Acute irritation, dermal sensitization, and occupational asthma have been reported in workers exposed to HDI. Respiratory effects of MDI or HDI have been reported in several human case reports and epidemiologic studies (spray painters or urethane molding workers), however, these studies are difficult to use (e.g., lack of exposure data) to establish dose-response relationships for these workplace exposures.

### 3.1.1 Key and Supporting Studies

#### *3.1.1.1 Key Studies*

##### 3.1.1.1.1 MDI Key Study - Pauluhn et al. (1999)

In Pauluhn et al. (1999), a single exposure study and a repeated 2-week (wk) nose-only inhalation study were conducted to examine the pulmonary response of rats to respirable PMDI. The single exposure study was designed to assess pulmonary irritation, and groups of male Wistar rats (6/group) were exposed to 0 (conditioned air), 2.4, 6.7, 15.8, or 38.7 mg PMDI/$m^3$ (analytical concentrations). The TCEQ considers an indication of irritation itself as an adverse effect. Histopathological or other additional adverse changes need not also result in conjunction with irritation as toxicity factors should be based on mild/sensitive adverse effects such as mild irritation. By contrast, histopathological changes often indicate adverse effects of a more serious or severe nature (e.g., degenerative changes, necrosis). Generally, relative to mild irritation, a much higher and more toxic dose would be required to produce histopathology due to acute exposure to a respiratory irritant. The animals breathed conditioned dry air for approximately 30 minutes (min) prior to exposure to collect baseline respiratory rate and tidal volume data, followed by a 150-min exposure to respirable PMDI aerosol. Following exposure to 15.8 and 38.7 mg/$m^3$, respiratory rate was increased approximately 20% above the pre-exposure control values, while in the 2.4 and 6.7 mg/$m^3$ groups respiratory rates were indistinguishable from the air control group. However, pulmonary irritation, as measured by changes in tidal volume, was observed in all exposure groups during exposure starting at 30 min and continuing to 150 min, and the magnitude of change was dose-dependent. Exposure to 2.4 mg PMDI/$m^3$ caused minimal acute pulmonary irritation (usually <10% decrease in tidal volume relative to control during exposure, although up to ≈14% decrease at the 120-130 min time

point or at 90-100 min of exposure). Accordingly, a 1.5-hour (h) minimal lowest-observed-adverse-effect-level (LOAEL) of 2.4 mg/m$^3$ was identified from this acute exposure study (i.e., for an approximate 14% decrease in tidal volume in response to irritation at 90-100 min of exposure). The TCEQ notes that use of 6.7 mg/m$^3$ as a LOAEL (based on a >20% decrease in tidal volume at around 1-h of exposure) in conjunction with a standard LOAEL-to- NOAEL (no-observed-adverse-effect-level) uncertainty factor ($UF_L$) of 3 results in an essentially identical candidate point of departure (POD) as use of the minimal LOAEL of 2.4 mg/m$^3$ with the minimal $UF_L$ of 2.

In the 2-wk nose-only exposure study, groups of Wistar rats (17/sex/group) were exposed to 0 (conditioned air), 1.1, 3.3, or 13.7 mg respirable PMDI/m$^3$ (analytical concentrations with mass median aerodynamic diameter (MMAD) of 1.46-1.52 µm and geometric standard deviation (GSD) of 1.51-1.6), 6 h/day (d), 5 d/wk for 2 wks. The objective of this 2-wk inhalation study was to analyze early biochemical, functional, and morphological evidence of pulmonary effects to respirable PMDI aerosols. Rats exposed to 3.3 and 13.7 mg/m$^3$ PMDI experienced concentration-dependent signs of respiratory tract irritation. For example, analysis of bronchoalveolar lavage (BAL) fluid and BAL cells revealed changes indicative of mild inflammatory response and/or cytotoxicity in rats exposed to 13.7 mg/m$^3$, and the changes were characterized by statistically significantly increased activities of lactate dehydrogenase (LDH) (as a marker enzyme for general cytotoxicity), β-n-acetylglucosaminidase (β-NAC), lysosomal enzymes, and total protein. Analysis of BAL fluid did not reveal changes indicative of a marked inflammatory response or cytotoxicity in rats exposed to 1.1 and 3.3 mg/m$^3$. Statistically significant dose-dependent increases of gamma-glutamyltranspeptidase (gamma-GT, as a marker enzyme for damage and/or increased activity of Clara cells) were found in rats exposed to both 3.3 and 13.7 mg/m$^3$. Additionally, at PMDI concentrations as low as 3.3 mg/m$^3$, some rats displayed a transient and mild tachypnea, with a labored and irregular breathing pattern toward the end of the exposure period. Effects related to changes in phospholipids of BAL cells were observed in the 3.3 and 13.7 mg/m$^3$ exposure groups, while the staining of BAL fluid using the polychrome stain for polar phospholipids demonstrated a concentration-dependent, statistically significant increase of phospholipids in alveolar macrophages (AM) in all PMDI exposure groups. Increased BAL cell acid phosphatase activity (as a marker for the release of enzymes from activated or lysed phagocytes), phosphatidylcholine, and cell volume were observed in rats exposed to 3.3 and 13.7 mg/m$^3$. However, no evidence of an influx of inflammatory cells or AM was observed in either group. The investigators indicated that the histochemical quantification of AM stained positively for polar lipids was apparently more sensitive to detect an increase in incorporation of phospholipids than was the biochemical determination of phosphatidylcholine in total BAL cells. The authors suggested that changes in phospholipid homeostasis appear to occur at lower levels than those eliciting inflammation and cytotoxicity and that PMDI aerosol interacts with pulmonary surfactant, which in turn may

stimulate type II pneumocytes to increase their production of surfactant and to proliferate. The investigators stated that this change in phospholipid homeostasis led to stimulation and proliferation of pneumocytes and appears to be a generic, adaptive response to a great deal of inhaled particulate. The level of 1.1 mg/m$^3$ for changes in phospholipid homeostasis was considered the lowest-observed-effect-level (LOEL). A LOEL can be considered a NOAEL according to the TCEQ Guidelines (TCEQ 2015a). The levels of 1.1 and 3.3 mg/m$^3$, respectively, were reasonably considered by study authors to be the NOAEL and LOAEL for respiratory tract irritation and focal inflammatory lesions.

Light and transmission electron microscopy suggest that exposure to 3.3 and 13.7 mg/m$^3$ PMDI resulted in focal inflammatory lesions and an accumulation of refractile, yellowish-brownish material in AM with concomitant activation of type II pneumocytes. In the terminal bronchioles, a concentration-dependent increase of bromodeoxyuridine-labeled epithelial cells was observed in all PMDI exposure groups. Thus, a NOAEL and LOAEL of 1.1 and 3.3 mg/m$^3$, respectively, for focal inflammatory lesions were identified from this 2-wk study. This LOAEL is consistent with that for signs of respiratory irritation (discussed above) based on the 2-wk results.

In summary, a minimal LOAEL of 2.4 mg/m$^3$ for minimal acute pulmonary irritation was identified from the single exposure study. A NOAEL and LOAEL of 1.1 and 3.3 mg/m$^3$, respectively, for concentration-dependent signs of respiratory tract irritation and focal inflammatory lesions were identified from the 2-wk study. Thus, the 1.5-h LOAEL of 2.4 mg/m$^3$ for minimal acute pulmonary irritation, which falls between the NOAEL and LOAEL of 1.1 and 3.3 mg/m$^3$ for signs of respiratory irritation and focal inflammatory lesions from the 2-wk study, has been identified as a candidate POD for the 1-h ReV. Results from the 2-wk study are not the most relevant data available for derivation of a 1-h ReV since the study exposure duration significantly exceeds the exposure duration of interest (i.e., 1 h versus 6 h/d, 5 d/wk for a total of 14-15 exposures or 84-90 h). In Pauluhn et al. (1999), the effects occurring due to 1.5-h of exposure are most relevant for derivation of the acute (i.e., 1-h) ReV.

### 3.1.1.1.2 HDI Key Study – Lee et al. 2003

In a study assessing acute inhalation of polymeric HDI aerosol (Lee et al. 2003), 2-6 month old male C57BL/6 mice (4-6/group) were exposed to concentrations of 0, 1, or 10 mg/m$^3$ (target concentrations) respirable HDI-BT aerosol for 5 hours (h) and were evaluated 0, 6, 18, 42, 90, 186, and 378 h after the end of exposure. The mean analytical concentrations (± standard deviation) were 1.30 ± 0.16 and 10.83 ± 0.62 mg/m$^3$ with MMAD ± GSD of 0.81 ± 1.2 and 1.96 ± 1.25 µm, respectively, for the low and high HDI-BT exposure groups. Concentrations of HDI monomer in the HDI-BT atmospheres were < 1.6%. Lung injuries were assessed by pulmonary function, lung weight, protein leakage, inflammatory cell influx, and lung lesions. The results

showed that mice exposed to HDI-BT exhibited dose-dependent, statistically significant changes in the following endpoints, with a greater magnitude of effect in the 10.83 mg/m$^3$ group compared to the 1.3 mg/m$^3$ group:

- Decrease in breathing frequency was observed in mice exposed to 10.83 mg/m$^3$, but not to 1.3 mg/m$^3$, immediately after (0 h) and 6 h after exposure and had returned to normal by 42 h.
- Increase in enhance pause (Penh) was observed in mice exposed to 1.3 or 10.83 mg/m$^3$. Penh peaked immediately after (0 h) and 6 h after exposure then progressively declined and returned to normal by 6 and 42 h, respectively, after 1.3 and 10.83 mg/m$^3$ exposure.
- Lung weights and lavage fluid protein content increased in both exposure groups and peaked at 6 and 18 h after 1.3 or 10.83 mg/m$^3$ exposure, respectively. Mice exposed to 10.83 mg/m$^3$ HDI-BT exhibited a 58-fold increase of protein concentrations over unexposed mice.
- Total cells and macrophages recovered in lavage fluid increased and peaked 90 h after exposure and returned to control levels by 186 and 378 h post exposure in the low and high concentration group, respectively.
- Neutrophils recovered in lavage fluid were increased at 6, 18, 42, and 90 h after exposure and peaked at 42-90 h after exposure in the high dose group.
- Proliferative lesions were observed and maximal at 90 h after exposure in mice exposed to 10.83 mg/m$^3$ HDI-BT.
- Increased percentages of BrdU-labeled cells in alveolar duct bifurcations and terminal bronchioles were observed at 90 h after exposure in both groups of exposed mice. Mice exposed to 10.83 mg/m$^3$ HDI-BT showed significantly more BrdU-labeled cells at these sites than mice exposed to 1.3 mg/m$^3$ HDI-BT.

In summary, the single 5-h inhalation exposure of mice to 1.3 or 10.83 mg/m$^3$ HDI-BT resulted in dose-dependent, statistically significant effects including increased lung weight and lavage fluid protein content, an influx of neutrophils, and a decrease in macrophages. A free-standing LOAEL of 1.3 mg/m$^3$ HDI-BT aerosol for increased lung weight, pulmonary inflammation and functional impairment was identified from this study. The free-standing 5-h LOAEL was identified as a candidate POD for derivation of the acute ReV.

### *3.1.1.2 Supporting Studies*

### 3.1.1.2.1 MDI Supporting Studies

#### *3.1.1.2.1.1 Pauluhn (2000)*

In an acute nose-only inhalation toxicity time course study by Pauluhn (2000), groups of 2-month old female Wistar rats (6-7/group/lapsed time after exposure) were exposed to 0

(conditioned air), 0.7 ± 0.07, 2.4 ± 0.26, 8 ± 0.47, or 20 ± 1.25 mg respirable PMDI aerosol/$m^3$ (analytical concentrations) for 6 h. The PMDI used in this study contained ~50% 4,4'-MDI, ~4% 2,4'-MDI, ~34% 3-oligomeric MDI, and ~9% 4-oligomeric MDI. The MMAD and GSD were described in the Pauluhn et al. (1999) study. All experiments and procedures described were performed in compliance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice (GLP) requirements. The time-response relationship of MDI-induced acute lung injury was examined at 0 h (directly after cessation of exposure), 3 h, 1 d, 3 d, and 7 d after exposure. BAL fluid was analyzed for markers (e.g., enzyme activities and protein) indicative of injury of the bronchoalveolar region. Phosphatidylcholine and acid phosphatase were measured in BAL fluid and cells. Glutathione was measured in BAL fluid and lung tissue. Statistically significant changes were not observed in body weight, necropsy findings, or relative or absolute lung weights. Total cell count in BAL fluid was transiently elevated in rats exposed to 8 and 20 mg/$m^3$ but the increase was not statistically significant. Statistically significant changes, however, were found in the following endpoints:

- Concentration of phospholipids in BAL cells, but not in BAL fluid, demonstrated a dose-dependent, statistically significant increase in groups exposed to ≥ 2.4 mg/$m^3$ at 1 d post-exposure, although at 3 h post-exposure the statistical increases were not monotonic (e.g., the response at 20 mg/$m^3$ was less than that at 2.4 or 8 mg/$m^3$).
- Total cell count in BAL fluid was significantly elevated in rats exposed to 20 mg/$m^3$ only on day 3 after exposure.
- An increased activity of alkaline phosphatase (to detect the release of enzymes from activated or lysed phagocytes) in BAL fluid was observed, although at 0 and 3 h post-exposure the statistical increases were not monotonic, and returned to control levels at 3 h (0.7 and 2.4 mg/$m^3$ group), day 1 (8 mg/$m^3$ group), or day 3 (20 mg/$m^3$ group) post-exposure.
- An increase of angiotensin-converting enzyme (ACE) activity in BAL fluid was observed in rats exposed to PMDI concentrations ≥ 2.4 mg/$m^3$.
- An increase of total protein in all exposure groups in BAL fluid at 0 and 3 h post-exposure, with the same response at 0.7 and 2.4 mg/$m^3$ at 0 h and a slightly greater response at 0.7 mg/$m^3$ than 2.4 mg/$m^3$ at 3 h (non-monotonic dose-response); total protein returned to control levels on day 1 (0.7 mg/$m^3$ group) and day 3 (≥ 2.4 mg/$m^3$) post-exposure.

In summary, following a single 6-h exposure, transient increases of total cell count, total protein, and enzyme activities in BAL fluid were observed at PMDI levels as low as 0.7 mg/$m^3$. In a personal communication with the European Chemicals Bureau (ECB 2005), the investigators further indicated that the transient dysfunction of the pulmonary epithelial barrier that occurred at a level as low as 0.7 mg/m³ could be interpreted as a dysfunction of pulmonary surfactant, thought to correspond to an adaptive response. DFG (2008) stated that such effects

are attributed to transient destabilization of surfactant and are not regarded as adverse because of the rapid reversibility of increased protein exudation. Relevant adverse changes were observed in the BAL fluid at PMDI exposure concentrations of 2.4 mg/m$^3$. The levels of 0.7 and 2.4 mg/m$^3$ are considered NOAEL and LOAEL, respectively. The 6-h LOAEL of 2.4 mg/m$^3$ was consistent with the LOAEL of 2.4 mg/m$^3$ identified from the Pauluhn et al. (1999) key study. Additional discussion of these results in the context of results from other studies can be found in Section 3.1.3.

#### *3.1.1.2.1.2 Reuzel et al. (1994a)*

In a short-term inhalation toxicity study with respirable PMDI aerosol by Reuzel et al. (1994a), groups of Wistar rats (10/sex/group) were exposed, whole body, to PMDI aerosol for 6 h/d, 5 d/wk, for 2 wks. The overall mean concentrations were 0 (control), 2.2, 4.9, or 13.6 mg/m$^3$. Ninety-five percent of the particles had an MMAD below 5 µm. Seven males and one female from the 13.6 mg/m$^3$ exposure group died. Severe respiratory distress and a significant decrease in body weight gain were observed in male and female rats exposed to 13.6 mg/m$^3$. Much less severe signs of respiratory distress and only slightly reduced body weight gain were observed in male rats exposed to 4.9 mg/m$^3$. Lung-to-body weight ratios were significantly higher in the mid- and high-concentration groups relative to controls. A NOAEL and LOAEL of 2.2 and 4.9 mg/m$^3$, respectively, for an increase in lung-to-body weight ratio were identified from this study.

#### *3.1.1.2.1.3 Kilgour et al. (2002)*

Kilgour et al. (2002) conducted both acute and subacute nose-only inhalation exposures to PMDI aerosols. For the acute exposure, groups of female Alpk:APfSD rats (40/group) were exposed to target concentrations of 0, 10, 30 or 100 mg/m$^3$ PMDI for 6 h. The corresponding MMAD ± GSD for exposure groups were 1.09 ± 1.48, 1.25 ± 1.54, and 0.96 ± 1.60 µm, respectively. At 1, 3, 10, or 30 d following exposure, 5 rats from each group were taken for analysis of lung lavage components and an additional 5 rats for a pathological examination. Following acute exposures, clinical signs were observed in all animals exposed to 10, 30, or 100 mg/m$^3$. The rats experienced an inflammatory phase, characterized by a large influx of inflammatory cells and soluble markers of inflammation (e.g., LDH and protein), increased lung surfactant, increased cell proliferation, and histological changes (AM accumulation, pneumonitis, airway proteinaceous effusion, cell exudate in bronchiolar lumen), followed by a rapid recovery. Most effects were concentration-dependent and had resolved by 10 d following exposure and virtually full resolution was seen after 30 d. A LOAEL of 10 mg/m$^3$ was identified from the 6-h acute exposure.

In the subacute exposure study, groups of female rats (30/group) were exposed nose-only to target concentrations of 0, 1, 4, or 10 mg/m$^3$ PMDI aerosols for 6 h/d, 5 d/wk, for 4 wks. The

corresponding MMAD ± GSD for exposure groups were 1.14 ± 2.47, 1.61 ± 1.95, and 1.09 ± 1.68 µm, respectively. The day following the last exposure and after a 30-d recovery period, 5 rats from each group were taken for analysis of BAL components, 5 for determination of total phospholipid concentrations in the soluble and cellular components of BAL fluid, and 5 for pathological examination. There were no clinical signs or body weight changes, but an increase in lung weight was seen the day following the last exposure in animals exposed to 10 mg/m$^3$, which had resolved following the 30-d recovery period. Analysis of BAL fluid showed statistically significant changes in total cell count and AM only at 10 mg/m$^3$. The polymorphonuclear leukocytes (PMNs) and lymphocytes/other cell types showed concentration-related and statistically significant increases at both 4 and 10 mg/m$^3$. At both 10 and 4 mg/m$^3$, dose-related increased numbers of 'foamy' macrophages were seen in the cell pellet, correlating with the increased analyzed phospholipid content of the pellet. Of the BAL fluid biochemical parameters, there was a statistically significantly increase in total protein and alkaline phosphatase activity at the end of the exposure period in animals exposed to 10 mg/m$^3$ PMDI. Almost all observed effects had resolved by 30 d post-exposure. Histologically, bronchiolitis and thickening of the central acinar regions were still present at 30 d post-exposure in the 10 and 4 mg/m$^3$ exposure groups. A NOAEL and LOAEL of 1 and 4 mg/m$^3$, respectively, for various effects (e.g., bronchiolitis, differential cell counts, influx of inflammatory cells, increases of LDH and protein in BAL fluid) were identified from this subacute study.

#### *3.1.1.2.1.4 Weyel and Schaffer (1985)*

In a short-term pulmonary irritation study by Weyel and Schaffer (1985), groups of male Swiss-Webster mice (4 /group) were exposed to MDI aerosol (MMAD ± GSD = 0.7 ± 1.6 µm) at mean analytical concentrations of 6.7, 10.2, 19.6, 25.8, 40.3, or 58.5 mg/m$^3$ for 4 h. An additional group of 8 mice was used as a control group. Average respiration rate was monitored before, during, and after exposure. Lung weights were measured 24 h post exposure. The results showed dose-response relationships for both a decrease in respiration rate and an increase in lung weights after 4 h of exposure. Percentage of lung weight increase compared to the control was approximately 9 and 20%, respectively, in the 6.74 and 10.2 mg/m$^3$ groups. The lung weight increase reached 42% in the 58.5 mg/m$^3$ group. The authors determined that the concentration required to decrease the respiration rate by 50% ($RD_{50}$) due to pulmonary irritation was 32 mg/m$^3$ MDI. A NOAEL and LOAEL for increase in lung weights of 6.7 and 10.2 mg/m$^3$ were identified from this study.

### 3.1.1.2.2 HDI Supporting Studies

#### *3.1.1.2.2.1 Ma-Hock et al. (2007)*

Groups of 8 wk-old male Wistar rats (5/group) were exposed for 6 h (nose-only) to two respirable polymeric emulsifier-modified HDI aerosol atmospheres, at analytical concentrations

of 0, 0.5, 2.7, 16.3, or 56.0 mg/m$^3$ for Test Substance I (polymeric emulsifier modified) and 0, 0.83, 3.03, or 16.7 mg/m$^3$ for Test Substance II (oligomeric allophanate modified), followed by serial sacrifices at 1, 3, and 7 d post-exposure. The MMAD ± GSD were 2.2-2.6 ± 1.7-2.0 µm and 1.8-2.3 ± 1.8-2.0 µm, respectively, for Test Substance I and II. Small amounts of monomeric HDI were detected in the vapor and aerosol phases for both test substances. BAL fluid was analyzed for biochemical and cytological markers indicative of bronchoalveolar region injury. After exposure to Substance I, statistically significant increases of total protein were observed in rats sacrificed 1 d following exposure to 2.7 mg/m$^3$ or higher. At 16.3 mg/m$^3$ or higher, statistically significant increases of LDH and gamma-GT were observed in rats sacrificed 1 d post-exposure. Changes were fully reversible within 7 d after exposure. A NOAEL of 0.5 and 2.7 mg/m$^3$ for the increase of total protein and LDH/GGT activities, respectively, were identified from the Substance I study. For Substance II, statistically significant increases of total protein or gamma-GT were observed in rats sacrificed 1 d following exposure to 16.7 mg/m$^3$. Statistically significant increases of LDH were only observed in rats sacrificed 7 d following exposure to 3.03 but not to 16.7 mg/m$^3$. A NOAEL and LOAEL of 3.03 mg/m$^3$ and 16.7 mg/m$^3$, respectively, for the increase of total protein and gamma-GT activities were identified from the Substance II study.

The results of this study showed that exposure of rats to Test Substance I and II caused dose-dependent lung irritation with increases of biochemical and cytological markers in BAL fluid. The increase of total protein is the most sensitive marker indicative of injury of the bronchoalveolar region. NOAELs of 0.5 and 3.03 mg/m$^3$ for increased total protein were identified for Test Substance I and II, respectively. The NOAEL of 0.5 mg/m$^3$ for increases of total protein is much lower than that of 3 mg/m$^3$ for histopathological changes in the subacute study by Pauluhn and Mohr (2001). Ma-Hock et al. (2007) further calculated NOAELs based on the relative increase of total protein in BAL fluid in concentration-effect curves with the removal of concentration points with effects near the control range. The extrapolated NOAEL for an increase of total protein for Test Substance I was 1.1 mg/m$^3$ and for Test Substance II was 2.3 mg/m$^3$. The extrapolated NOAELs support the use of the free-standing LOAEL of 1.3 mg/m$^3$ for pulmonary inflammation and functional impairment identified from the Lee et al. (2003) key study.

#### *3.1.1.2.2.2 Pauluhn (2000, 2002)*

In a single 6 h inhalation exposure study, groups of female Wistar rats (6/group/sacrificed time after exposure) were exposed to respirable polymeric HDI isocyanurate-type aerosol (HDI-IC, a mixture that contains approximately 50% trimeric HDI) in concentrations of 0, 3.9, 15.9, 54.3, or 118.1 mg/m$^3$. The MMAD ± GSD was 1.7-2.0 ± 1.5 µm. All experiments and procedures described were performed in compliance with the OECD GLP requirements. BAL fluid samples were taken directly after cessation of exposure (0 h) and 3 h, 1 d, 3 d, and 7 d post-exposure. BAL determinations included total cell count in BAL fluid, total protein, ACE, and LDH.

Statistically significant increases of total protein and ACE were observed in rats sacrificed 3 h and 18 h following exposure to 3.9 mg/m$^3$ HDI-IC aerosol or higher. Most changes were reversible within the post-exposure period. The level of 3.9 mg/m$^3$ was a free-standing LOAEL. A clear concentration-effect relationship was established for total protein and ACE. Based on these most sensitive endpoints in BAL fluid, a single-exposure benchmark no-effect threshold concentration of 3 mg/m$^3$ for minimal acute pulmonary irritation was estimated for the HDI-IC aerosol by the investigator. The minimal free-standing LOAEL (3.9 mg/m$^3$) is higher than the free-standing LOAEL of 1.3 mg/m$^3$ for increased lung weight, pulmonary inflammation and functional impairment discussed above.

#### *3.1.1.2.2.3 Pauluhn and Mohr (2001)*

In a 2-wk, repeated-dose inhalation study by Pauluhn and Mohr (2001), groups of 20 male Wistar rats were exposed nose-only to analytical concentrations of 1.2, 4.6, 16.31, or 69.2 mg/m$^3$ HDI-IC for 6 h/d, 5 d/wk for 2 wks. Ten rats/group were sacrificed at the end of the exposure period, and the remaining 10 rats/group were sacrificed 7 wks post-exposure. In rats sacrificed shortly after exposure, wet lung weights were mildly increased and the number of AM in BAL fluid was significantly increased at 69.2 mg/m$^3$. Other respiratory tract endpoints (histopathological lesions, measurements of arterial blood gases, lung function tests, and analysis of BAL fluid) were not significantly different between the control group and any of the exposure groups.

In a 3-wk dose range-finding study by Pauluhn and Mohr (2001), groups of 10 Wistar rats/sex/level were exposed nose-only to target concentrations of 3, 15, or 75 mg/m$^3$ HDI-IC or HDI-BT for 6 h/d, 5 d/wk for 3 wks. All experiments and procedures described were performed in compliance with the OECD testing guideline 412. Following exposure, compound-related effects were found at the intermediate- and high-level exposure groups and were confined to mild respiratory distress, marginally decreased body weights, and increased lung weights. Wet lung weights of exsanguinated rats were significantly increased in both the intermediate- and high-level exposure groups. Histopathology demonstrated dose-dependent increases of AM influx, focal interstitial fibrosis with round-cell infiltrations, and BAL cell proliferation in the high-level exposure groups ($p<0.01$). At the intermediate exposure level, only hyperplasia in the larynx and trachea and AM influx were observed to a minor extent ($p<0.05$). Appreciable differences between the two types of polyisocyanates were not observed. The NOAELs and LOAELs for pulmonary irritation and increases in lung weights were 3.7-4.3 and 14.7-17.5 mg/m$^3$ (analytical concentrations), respectively. The subacute LOAELs of 14.7-17.5 mg/m$^3$ were higher than the free-standing LOAEL of 1.3 mg/m$^3$ identified from the 5-h Lee et al. (2003) key study.

### *3.1.1.3 Reproductive and Developmental Studies*

#### 3.1.1.3.1 MDI Reproductive and Developmental Studies

No studies were identified that investigated the reproductive and/or developmental effects of MDI or PMDI aerosol inhalation exposure in humans. Gravid Wistar rats (23-26/group) were exposed by whole-body inhalation to clean air (control) or to monomeric 4,4'-MDI (MMAD ± GSD = 1.1 ± 1.37 µm) at 1, 3, or 9 mg/m$^3$ for 6 h/d from gestational day (GD) 6-15 (Buschmann et al. 1996). Rats were sacrificed on GD 20. The absolute and relative lung weights in the high-dose group of dams were significantly increased (23%) compared with the control animals. Treatment did not influence any other maternal or fetal parameters investigated, although a slight but significant increase in litters with fetuses displaying asymmetric sternebrae was observed after treatment with the highest dose. However, the investigators indicated that the number of effects observed in the 9 mg/m$^3$ group was within the limits of biological variability. Nevertheless, the authors indicated that a PMDI-induced effect in the 9 mg/m$^3$ group cannot be excluded and thus determined a NOAEL and LOAEL of 3 and 9 mg/m$^3$, respectively, for embryotoxic effects in this study.

In a well-conducted developmental range-finding study, conducted according to OECD Guideline 414, mated female Wistar rats (8/group) were exposed to PMDI by whole-body inhalation at exposure levels of 0, 2, 8, or 12 mg/m$^3$ for 6 h/d from GD 6-15 (Waalkens-Berendsen and Arts 1992 as cited in IPCS 2000). The mean number of corpora lutea, implantation sites, early and late resorptions, and, consequently, pre- and post-implantation loss showed no statistically significant differences among the control and treated groups. No external treatment-related abnormalities were observed in the fetuses. The only observed maternal toxicity was increased lung weights and decreased food intake in the 12 mg/m$^3$ group. A NOAEL of 8 mg/m$^3$ and a LOAEL of 12 mg/m$^3$ for maternal toxicity and a free-standing NOAEL of 12 mg/m$^3$ for developmental toxicity were identified from this study.

In a prenatal PMDI toxicity study by Gamer et al. (2000) conducted according to OECD Guideline 414, 61-70 d old mated female rats (25/group) were exposed to concentrations of 1, 4, or 12 mg/m$^3$ (MMAD < 2.8 µm) PMDI for 6 h/d from GD 6-15. Maternal toxicity was observed at 12 mg/m$^3$, including mortality (2 of 24 pregnant dams), damage to the respiratory tract, reduced body weights and weight gain, and reduced liver and increased lung weights. Also in this group, statistically significant decreases in placental and fetal weights occurred, and a significant increase in fetuses/litters with changes in incidence of skeletal variations and retardations (affected fetuses/litter) was observed. Mean percentages for skeletal variations were 38.9, 48.7, 47.8, and 63.2% ($p<0.01$), and mean percentages for overall variations were 24.6, 34.7 ($p<0.05$), 33.4 ($p<0.05$), and 40.0% ($p<0.01$), at 0, 1, 4, and 12 mg/m$^3$, respectively. No statistically-significant treatment-related abnormalities were observed in dams or fetuses at 1

and 4 mg/m$^3$. The NOAEL and LOAEL for maternal and fetal toxicity as well as for developmental effects were 4 and 12 mg/m$^3$, respectively.

The LOAELs (≈9-12 mg/m$^3$) identified in these reproductive/developmental toxicity studies are, for example, appreciably higher than the 1.5-h LOAEL of 2.4 mg/m$^3$ for minimal acute pulmonary irritation from the Pauluhn et al. (1999) key study.

#### 3.1.1.3.2 HDI Reproductive and Developmental Studies

No studies were identified regarding the reproductive and/or developmental effects of HDI aerosol exposure in humans or animals.

## 3.1.2 Mode of Action (MOA) Analysis and Dose Metric

Isocyanates are reactive toward nucleophiles and readily form adducts with peptides, proteins, and nucleic acids. Therefore, isocyanates often elicit a characteristic portal-of-entry (POE) effect (Pauluhn 2000a). The MOA for the acute lung irritation-based point of departure (POD) due to MDI or HDI aerosol exposure likely occurs at the site of initial aerosol deposition and involves the parent compound, rather than a metabolite (Pauluhn 2011, 2002b). The MOA for an acute lung irritation-based POD is likely to be based on the high reactivity of the diisocyanate group (DFG 2013). Thus, exposure concentration of the MDI or HDI aerosol will be used as the dose metric.

## 3.1.3 Selection of the Key Study, POD and Critical Effect

### *3.1.3.1 Selection of the Key Study for MDI, Aerosol*

Table 8 is a summary of the acute and subacute inhalation and reproductive/developmental toxicity studies for MDI aerosol. Selection of the acute critical effect for MDI aerosol and the corresponding candidate POD for derivation of an acute ReV applicable to both MDI and HDI is discussed below.

Pauluhn (2000) reports statistically increased alkaline phosphatase and total protein in Wistar rat BAL fluid at ≤ 1 day following 6 h exposure to 0.7, 2.4, 8, or 20 mg/m$^3$ PMDI, as well as statistically increased LDH in BAL fluid 3 h post-exposure. However, these data generally lacked a monotonic dose-response. Moreover, statistically significant increases in alkaline phosphatase and total protein at 0.7 and 2.4 mg/m$^3$ appear inconsistent with results from: (1) Pauluhn et al. (1999), who did not report statistically increased alkaline phosphatase, total protein, or LDH following 2-wk exposure (6 h/d, 5 d/wk) of Wistar rats to 3.3 mg/m$^3$; and (2) Kilgour et al. (2002), who reported BAL fluid parameter effects 1 d following a 4 wk exposure of rats to 10 mg/m$^3$ (i.e., moderate increases in total protein, LDH, alkaline phosphatase, phospholipids) but not at 1 or 4 mg/m$^3$. As a more specific example, Pauluhn (2000) reported statistically

increased total protein in BAL fluid at approximately 150% of the control value at 2.4 mg/m$^3$ for the 0 h, 3 h, and 1 d post-exposure time points, whereas a similar statistically significant increase of 147% occurred only at 13.7 mg/m$^3$ 1 d post-exposure in the Pauluhn et al. (1999) subacute study. In Pauluhn et al. (1999), statistically significant increases in LDH and total protein (but not alkaline phosphatase) only occurred in Wistar rats exposed to 13.7 mg/m$^3$ for 2 wks, although gamma-GT as well as several BAL cell endpoints (e.g., acid phosphatase) were statistically increased at ≥ 3.3 mg/m$^3$ (Pauluhn et al. 1999). The study authors indicate that exposure to ≥ 3.3 mg/m$^3$ PMDI resulted in concentration-dependent signs of respiratory tract irritation and focal inflammatory lesions (as well as the accumulation of refractile, yellowish-brownish material in AM with concomitant activation of type II pneumocytes). For example, some rats of the 3.3 mg/m$^3$ group displayed a transient and mild tachypnea, with a labored and irregular breathing pattern toward the end of the exposure period. Additionally, the study reported minimal acute pulmonary irritation as evidenced by tidal volume decreases at 2.4 mg/m$^3$ (usually <10% decrease in tidal volume relative to control during exposure, although up to ≈14% decrease between 90-100 min of chemical exposure). Based on the result of this single exposure study, study authors concluded that stimulation of minimal pulmonary irritant receptors can occur at exposure levels in the range of 2.4 mg/m$^3$. This exposure level is reasonably consistent with the LOAEL of 3.3 mg/m$^3$ for respiratory tract irritation and focal inflammatory lesions identified from the 2-wk study; and is about half that which caused statistically increased lung weights in Reuzel et al. (1994a) (i.e., a 2-wk LOAEL of 4.9 mg/m$^3$). Collectively, these data suggest a LOAEL for more clearly adverse acute/subacute effects (e.g., respiratory tract irritation, focal inflammatory lesions, increased relative lung weight) in the range of 2.4-4.9 mg/m$^3$, the lower end of which identifies the critical effect for MDI aerosol and a candidate POD for acute ReV derivation. Since 2-wk study results are not most relevant for derivation of a 1-h ReV, the free-standing 1.5-h LOAEL of 2.4 mg/m$^3$ (Pauluhn et al. 1999) was used as a candidate POD for derivation of an acute ReV applicable to both MDI and HDI.

**Table 8. Summary of Acute and Subacute Inhalation Studies for MDI Aerosol**

| Species (n/sex) | Exposure Concentration | Exposure Duration | NOAEL | LOAEL | Notes (References) |
|---|---|---|---|---|---|
| Wistar rats (6 M/group) | 0, 2.4, 6.7, 15.8, or 38.7 mg/m$^3$ | 150 min | --- | 2.4 mg/m$^3$ | Minimal acute pulmonary irritation at 90-100 min of chemical exposure (Pauluhn et al. 1999) |
| Wistar rats (17/sex/ group) | 0, 1.1, 3.3, or 13.7 mg/m$^3$ | 6 h/d, 5 d/wk for 2 wk | 1.1 mg/m$^3$ | 3.3 mg/m$^3$ | Focal inflammatory lesions, concentration-dependent signs of respiratory tract irritation in BAL fluid, abnormal breathing (Pauluhn et al. 1999) |
| Wistar rats (6-7 F/group) | 0, 0.7, 2.4, 8, or 20 mg/m$^3$ | 6 h | 0.7 mg/m$^3$ | 2.4 mg/m$^3$ | Transient, non-monotonic increases in BAL fluid components as low as 0.7 mg/m$^3$, acute pulmonary irritation (e.g., decreased tidal volume) at 2.4 mg/m$^3$ during 150-min exposure (e.g., Fig. 14, Pauluhn 2000) |
| Wistar rats (10 M, 10 F) | 0, 2.2, 4.9, or 13.6 mg/m$^3$ | 6 h/d, 5 d/wk for 2 wk | 2.2 mg/m$^3$ | 4.9 mg/m$^3$ | Increase in lung-to-body weight ratio (Reuzel et al. 1994a) |
| Alpk:APfSD rats (40 F/group) | 0, 10, 30, or 100 mg/m$^3$ | 6 h | --- | 10 mg/m$^3$ | Histopathological changes (e.g., pneumonitis), large influx of inflammatory cells, and increases of LDH and protein in BAL fluid (Kilgour et al. 2002) |
| Alpk:APfSD rats (30 F/group) | 0, 1, 4, or 10 mg/m$^3$ | 6 h/d, 5 d/wk for 4 wks | 1 mg/m$^3$ | 4 mg/m$^3$ | Histopathological changes (e.g., bronchiolitis), increases in AM, PMNs and lymphocytes/other cell types in BAL fluid (Kilgour et al. 2002) |
| Swiss-Webster mice (4 M/group) | 0, 6.7, 10.2, 19.6, 25.8, 40.3, or 58.5 mg/m$^3$ | 4 h | 6.7 mg/m$^3$ | 10.2 mg/m$^3$ | Increase in lung weights (Weyel and Schaffer 1985) |
| Gravid Wistar rats (23-26/ group) | 0, 1, 3, or 9 mg/m$^3$ | 6 h/d from GD 6-15 | 3 mg/m$^3$ | 9 mg/m$^3$ | Increases in lung weights for maternal toxicity; increases in litters with fetuses displaying asymmetric sternebrae (Buschmann et al. 1996) |
| Mated female Wistar rats (25/group) | 0, 1, 4, or 12 mg/m$^3$ | 6 h/d from GD 6-15 | 4 mg/m$^3$ | 12 mg/m$^3$ | Maternal (mortality, respiratory tract damage, reduced liver and body weight, increased lung weight) and fetal (decreased placental/fetal weights, skeletal retardations) toxicity (Gamer et al. 2000) |
| Mated female Wistar rats (8/group) | 0, 2, 8, or 12 mg/m$^3$ | 6 h/d from GD 6-15 | 8 mg/m$^3$ | 12 mg/m$^3$ | Maternal toxicity (increased lung weights and decreased food intake) |
| | | | 12 mg/m$^3$ | --- | Developmental toxicity not observed (Waalkens-Berendsen and Arts 1992) |

### *3.1.3.2 Selection of the Key Study for HDI, Aerosol*

Table 9 is a summary of acute and subacute inhalation studies for polymeric HDI aerosol exposure. The table shows that the use of the free-standing LOAEL (1.3 mg/m$^3$) identified by Lee et al. (2003) as a candidate POD for acute ReV derivation is more appropriate than those from supporting studies for the following reasons:

- The effects observed for pulmonary inflammation and functional impairment are more clearly adverse than those observed for total protein and enzyme activities;
- The NOAEL (0.5 mg/m$^3$) identified from Ma-Hock et al. (2007) for increase of total protein in rats exposed to Test Substance I was not supported by the results from exposure to Test Substance II from the same study;
- The increase of total protein from Ma-Hock et al. (2007) was considered minimal and transient;
- Other NOAELs identified from supporting studies are in the range of 2.7–3 mg/m$^3$; and
- The extrapolated NOAEL for the free-standing minimal LOAEL of 1.3 mg/m$^3$ would be 0.45 mg/m$^3$ by applying an uncertainty factor of 3 for the extrapolation of LOAEL to NOAEL.

**Table 9. Summary of Acute and Subacute Inhalation Studies for HDI Aerosol**

| Species (n/sex) | Exposure Concentration | Exposure Duration | NOAEL | LOAEL | Notes (References) |
|---|---|---|---|---|---|
| C57BL/6 mice (4-6 M/group) | 0, 1.3, or 10.8 $mg/m^3$ respirable HDI-BT | 5 h | --- | 1.3 $mg/m^3$ | Dose-related increased lung weight, and pulmonary inflammation and functional impairment (Lee et al. 2003) |
| Wistar rats (5 M/group) | 0, 0.5, 2.7, 16.3, or 56.0 $mg/m^3$ (Test Substance I) | 6 h | 0.5 $mg/m^3$ | 2.7 $mg/m^3$ | Transient increases in total protein in BAL fluid recovered within 7 d post exposure (Ma-Hock et al. 2007) |
| | | | 2.7 $mg/m^3$ | 16.3 $mg/m^3$ | Increases in LDH and gamma-GT activities in BAL fluid recovered within 7 d post exposure (Ma-Hock et al. 2007) |
| Wistar rats (5 M/group | 0, 0.83, 3.03, or 16.7 $mg/m^3$ (Test Substance II) | 6 h | 3.03 $mg/m^3$ | 16.7 $mg/m^3$ | Increases in total protein and gamma-GT activities in BAL fluid 1 d post exposure (Ma-Hock et al. 2007) |
| Wistar rats (6 F/group) | 0, 3.9, 15.9, 54.3, or 118.1 $mg/m^3$ HDI-IC | 6 h | --- | 3.9 $mg/m^3$ | Increases in total protein and enzyme activities in BAL fluid (Pauluhn 2000, 2002) |
| Wistar rats (5/sex/group) | 3, 15, or 75 $mg/m^3$ HDI-IC or HDI-BT | 6 h/d, 5 d/wk for 3 wks | 3 $mg/m^3$ | 15 $mg/m^3$ | Increase in lung weights and decrease in body weights. Increases of AM influx, focal interstitial fibrosis with round-cell infiltrations in BAL fluid (Pauluhn and Mohr 2001) |

Therefore, for polymeric HDI aerosol, the free-standing 5-h LOAEL of 1.3 $mg/m^3$ from the Lee et al. (2003) study was identified as a candidate POD for derivation of an acute ReV applicable to both MDI and HDI. The critical effects were increased lung weight, and pulmonary inflammation and functional impairment in mice.

### *3.1.3.3 Selection of the Overall Key Study, POD, and Critical Effect*

The sections above identify two candidate PODs for the derivation of an acute (i.e., 1 h) ReV:

- A 1.5-h LOAEL of 2.4 mg/m$^3$ for mild acute pulmonary irritation (e.g., decreased tidal volume) from the Pauluhn et al. (1999) MDI aerosol rat study.

- A 5-h LOAEL of 1.3 mg/m$^3$ for pulmonary inflammation and functional impairment from the Lee et al. (2003) HDI aerosol mouse study.

While the 1.5-h LOAEL (2.4 mg/m$^3$) need not be duration adjusted to derive a 1-h ReV (e.g., see Section 3.1.4.1), the 5-h LOAEL conservatively adjusted to a 1-h concentration with Haber's rule as modified by ten Berge (1986) and an "n" of 3 (consistent with Section 4.2.2 of TCEQ 2015a) would result in an almost identical candidate POD (2.223 mg/m$^3$). However, because the studies were conducted in different laboratory animal species (i.e., rats, mice), the human equivalent concentrations (HECs) corresponding to these candidate PODs will differ and must be considered in selecting the key POD and critical effect(s). The regional deposition dose ratios (RDDRs) for these effects in rats and mice are 0.6789 and 1.993 (see Appendix 2 and Section 3.1.4.2), respectively. These RDDRs result in 1-h human equivalent concentration POD ($POD_{HEC}$) values of 1.6293 and 4.46 mg/m$^3$, respectively, for effects observed in the Pauluhn et al. (1999) and the Lee et al. (2003) studies. Consequently, the Pauluhn et al. (1999) rat study will be selected as the key study for acute ReV derivation as it has the lowest $POD_{HEC}$, with the critical effect being mild acute pulmonary irritation (e.g., decreased tidal volume) (TCEQ 2015a).

## 3.1.4 Dosimetric Adjustments

### *3.1.4.1 Exposure Duration Adjustments*

The POD from the Pauluhn et al. (1999) study is based on a free-standing 1.5-h minimal LOAEL of 2.4 mg/m$^3$ and will not be adjusted to a 1-h exposure duration. Thus, the $POD_{ADJ}$ is 2.4 mg/m$^3$ for the POD of 2.4 mg/m$^3$. [The TCEQ notes that use of 6.7 mg/m$^3$ as the 1-h LOAEL (based on a >20% decrease in tidal volume at around 1-h of exposure) in conjunction with a standard $UF_L$ of 3 would result in an essentially identical POD as use of the minimal LOAEL of 2.4 mg/m$^3$ with the minimal $UF_L$ of 2.]

### *3.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure*

Default dosimetric adjustments for animal-to-human exposure were conducted for the rat study to determine the calculated $POD_{HEC}$ for the critical endpoint. In the key study, an aerosol of PMDI 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 PMDI in the target respiratory region.

Of the available rat models, the asymmetric model for the Long-Evans rat was chosen for several reasons: (1) although the key study used Wistar rats, a corresponding Wistar rat model does not currently exist in the MPPD program; (2) historical precedent and consistency; (3) although humans have highly symmetric branching patterns, rodents have highly asymmetric branching patterns (EPA 2009); and (4) the current Sprague-Dawley Asymmetric model has a programming issue which results in utilizing some of the Long-Evans parameters (personal communication with Owen Price at Applied Research Associates, Inc). Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions. According to Pauluhn et al. (1999), the average MMAD of PMDI used in their study was 1.48 μm with an average GSD of 1.53, and the particle density was 1.23 g/cm$^3$ (Table 5). The chemical concentration is the $POD_{ADJ}$ of 2.4 mg/m$^3$. Because the critical effect was pulmonary irritation, the target region for PMDI was considered as the total particle distribution for tracheobronchial and pulmonary regions. The average body weights of the male rats from the 2-wk study (228.05 g) were used, since body weights were not listed for the single 150-min study and there was no statistically significant difference between the control and treated animals in the 2-wk study. Minute volume (166.69 mL/min), breathing frequency (102 breaths/min), and tidal volume (1.63 mL) were calculated using this average body weight. All remaining values used were default. Once the total particle distribution was determined (Appendix 2), the RDDR was calculated as follows:

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

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

- $V_E$ = minute volume
- DF = deposition fraction in the target region
- NF = normalizing factor (respective surface areas)
  - A = animal
  - H = human

RDDR = [166.69 mL/min / 13,800 mL/min] x [0.0596/0.1683] x [543,200 cm$^2$/3422.5 cm$^2$]
RDDR = 0.6789.

The RDDR was then used to dosimetrically-adjust the animal POD to a $POD_{HEC}$.

$$POD_{HEC} = POD_{ADJ} \times RDDR = 2.4 \text{ mg/m}^3 \times 0.6789 = 1.6294 \text{ mg/m}^3$$

### 3.1.5 Adjustments of the $POD_{HEC}$

The $POD_{HEC}$ of 1.6294 mg/m$^3$ was used to derive the acute ReV and $^{acute}$ESL for PMDI aerosol. The following UFs were applied to the $POD_{HEC}$ (Total UF = 60):

Health-Based Acute ReV and ESL for MDI and HDI, Aerosol

- $UF_H$ of 10 for intraspecies variability. A lower $UF_H$ is not supported as no data were identified suggesting that potentially sensitive subpopulations would be similarly sensitive to PMDI exposure as the general population;
- $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not potential toxicodynamic differences;
- $UF_L$ of 2 for extrapolation from the minimal LOAEL to a NOAEL; a higher $UF_L$ was not used because the LOAEL of 2.4 mg/m$^3$ is for minimal acute pulmonary irritation and falls between the NOAEL and LOAEL of 1.1 and 3.3 mg/m$^3$ for signs of respiratory irritation and focal inflammatory lesions from the 2-wk study, conservatively resulting in an estimated 1-h NOAEL value (2.4 mg/m$^3$ / 2 = 1.2 mg/m$^3$) that is nearly identical to the 2-wk NOAEL value (1.1 mg/m$^3$); and
- $UF_D$ of 1 was used in consideration of the overall database. Several acute or subacute animal studies were conducted for different toxicity endpoints in two species (rats, mice), and three reproductive/developmental rat studies are available for MDI (additional information is discussed below). Results from subacute studies for multiple-week exposure strongly support the conservativeness of the POD from the 150-min study for derivation of the 1-h ReV and ESL. For example, studies involving exposure 6 h/day, 5 d/wk for 2 or 4 wks produced respiratory tract LOAELs (3.3-4.9 mg/m$^3$) that are higher than the conservative, 150-min LOAEL (2.4 mg/m$^3$) used to derive the acute ReV, despite the exposure durations associated with effects being significantly longer (i.e., ≈60-120 times). Additionally, similar to HDI vapor being used as a toxicity surrogate for MDI vapor (see Section 3.2), acute/subacute toxicity studies of PHDI aerosol are available for two species and support the conservativeness of the PMDI aerosol POD. For example, the 5-h mouse LOAEL for HDI aerosol-induced respiratory tract effects (1.3 mg/m$^3$) compares favorably to the 150-min rat LOAEL (2.4 mg/m$^3$) considering that PMDI-induced effects had already begun 30 min into exposure (i.e., 5 h versus 0.5 h is a 10-fold difference in duration, whereas the LOAELs differ by less than a factor of 2). Other acute/subacute LOAELs for PHDI for exposure durations from 6 h to 6 h/d, 5 d/wk for 3 wks (i.e., total durations of 6-90 h) range from 2.7-16.7 mg/m$^3$ and are somewhat higher than that used to derive the acute ReV for PMDI (2.4 mg/m$^3$). Thus, acute/subacute data for both PMDI and PHDI aerosols strongly support the acute POD. Lastly, although reproductive/developmental study results are not available in another species, rat study results for both PMDI and HDI vapor support the conservativeness of the POD for the acute ReV. For example, the LOAELs (≈9-12 mg/m$^3$) identified in PMDI reproductive/developmental toxicity studies are appreciably higher than the LOAEL of 2.4 mg/m$^3$ for minimal acute pulmonary irritation from the Pauluhn et al. (1999) key study. This is not particularly surprising given the high reactivity of diisocyanates (e.g., with water), or that respiratory tract tissue doses of $^{14}$C-labeled MDI (µg equivalent of MDI per gram of tissue) were orders of magnitude higher than those in the gonads of male

Wistar rats at 0, 8, 24, and 168 h following exposure to 2 mg/m$^3$ aerosol for 6 h (Table III of Gledhill et al. 2005). Additionally, as another reactive diisocyanate, neither short- nor long-term reproductive/developmental rat studies for HDI vapor showed developmental or reproductive effects. For example, no reproductive/developmental/neurological effects were observed in Astroff et al. (2000b) at multiple-day, repeated exposure concentrations up to 2.033 mg/m$^3$ (6 h/d for 49 d), a reproductive/developmental NOAEL similar to the acute LOAEL POD for PMDI (2.4 mg/m$^3$). That is, like PMDI aerosol, respiratory tract effects appeared to be more sensitive for HDI vapor, another highly reactive diisocyanate. The reactivity of diisocyanates in conjunction with study results demonstrating respiratory tract effects at lower concentrations than, or in the absence of, developmental/reproductive effects mitigates concern about reproductive/developmental effects being more sensitive than respiratory tract effects. These considerations (i.e., acute PMDI studies in two species, subacute PMDI study results, acute/subacute study results for another diisocyanate (PHDI), reproduction/developmental study result LOAELs and NOAELs for PMDI and HDI vapor and their reactivity at the point of exposure) inform and support the acute POD for PMDI as conservative such that the acute ReV is expected to be protective against potential reproductive/developmental effects. Thus, the protectiveness of the acute POD for deriving the acute ReV for PMDI aerosol is strongly supported by considerable data. Accordingly, confidence in the database is considered high. The quality of the key rat study is high.

$$\text{Acute ReV} = POD_{HEC} / (UF_H \times UF_A \times UF_L \times UF_D)$$
$$= 1.6294 \text{ mg/m}^3 / (10 \times 3 \times 2 \times 1)$$
$$= 1.6294 \text{ mg/m}^3 / 60$$
$$= 0.02716 \text{ mg/m}^3$$
$$= 27 \text{ µg/m}^3 \text{ (rounded to two significant figures)}$$

### 3.1.6 Health-Based Acute ReV and $^{acute}$ESL, Aerosol

In deriving the acute ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV was then used to calculate the ESL, and the ESL was subsequently rounded.

The $^{acute}$ESL of 8.1 µg/m$^3$ for MDI and HDI aerosol is based on the acute ReV of 27 µg/m$^3$ multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 10).

**Table 10. Summary of Acute ReV and $^{acute}$ESL for MDI and HDI, Aerosol**

| Parameter | MDI and HDI Aerosol |
|---|---|
| Study | Pauluhn et al. (1999) |
| Study Quality | High |
| Study Population | Wistar male rats (6 M/group) |
| Exposure Method | Inhalation exposure to 0 (conditioned air), 2.4, 6.7, 15.8, or 38.7 mg/m$^3$ MDI |
| Exposure Duration | 150 min |
| Critical Effects | Mild acute pulmonary irritation (e.g., decreased tidal volume) |
| POD | 2.4 mg/m$^3$ (minimal LOAEL) |
| $POD_{ADJ}$ to 1h | 2.4 mg/m$^3$ (no adjustment, effects occurred at 1.5 h of exposure) |
| $POD_{HEC}$ | 1.6294 mg/m$^3$ (2.4 mg/m$^3$ x RDDR 0.6789) |
| Total UFs | 60 |
| *Intraspecies UF* | 10 |
| *Interspecies UF* | 3 |
| *LOAEL to NOAEL* | 2 |
| *Incomplete Database UF*<br>*Database Confidence* | 1<br>High |
| **Acute ReV [1 h] (HQ = 1)** | **27 µg/m$^3$** |
| **$^{acute}$ESL [1 h] (HQ = 0.3)** | **8.1 µg/m$^3$** |

## *3.2 Health-Based Acute ReV and ESL for MDI and HDI, Vapor*

The physicochemical properties of MDI and HDI vapor favor its retention in the upper airway and thus, MDI and HDI in the vapor phase primarily cause upper respiratory tract lesions (particularly in the nasal cavity) due to its reactivity and water solubility (Pauluhn 2008, 2015).

The only acute study available that examined inhalation exposure to monomeric MDI vapor is a subacute study for airway hyper-responsiveness conducted by Marek et al. (1999). In this study, groups of female guinea pigs (11/group) were exposed to 0, 5, 10, or 20 ppb MDI vapor for 6 h/d for 5 d. MDI vapors were generated in a gas-tight, heated (80-120°C), stainless steel container. Significant increases in airway hyper-responsiveness to acetylcholine (ACH) were observed in guinea pigs exposed to 10 or 20 ppb MDI ($p<0.005$) but not in the 5 ppb exposure group. The results showed a dose-dependent increase in ACH response. A NOAEL and LOAEL of 5 and 10 ppb, respectively, were identified by the investigators. The Marek et al. (1999) study was not considered a suitable basis for a minimal risk level (MRL) by the ATSDR because the study did not include a histological examination of the respiratory tract and it is possible that histological alterations, particularly in the nasal cavity, may occur at lower concentrations than airway hyper-responsiveness to ACH (ATSDR 2015). Additionally, the increased ACH responsiveness of tracheal smooth muscle due to MDI vapor as measured by isometric pressure ($P_{iso}$) to ACH solutions inside tracheal preparations (i.e., *ex vivo*) is not related by study authors to any degree of functional impairment (i.e., adversity).

In the Marek et al. (1999) study, four groups of animals (11/group) were similarly exposed to HDI vapor at 10 ppb for 1, 2, 4, or 8 wks. While the results showed that exposure to 10 ppb HDI vapor for 1 wk produced a similar level of response to ACH as MDI vapor (i.e., a $P_{iso}$ of 4.3 ± 0.61 kPa for HDI vapor compared to 4.05 ± 0.29 kPa for MDI), the study authors indicated that in the guinea pigs exposed to HDI vapor over a period of 8 wks, “Basic respiratory and cardiovascular parameters remained largely unaltered.”

Consistent with ATSDR, the TCEQ decided not to use the NOAEL identified from the Marek et al. (1999) study as a candidate POD for derivation of an acute ReV. For air permits review of MDI vapors, the acute ESL derived for HDI vapors will be used.

### 3.2.1 Key and Supporting HDI Studies

#### *3.2.1.1 Key Study – Kopf 2015*

In an unpublished 1-wk subacute pilot inhalation study conducted according to OECD Guideline 412 by Kopf 2015 (cited in ECHA 2019), groups of 10 young adult male Wister rats were exposed (nose-only) to 0, 0.02, 0.1, 0.5, and 2 ppm HDI vapor (exposure concentrations were targeted to bracket Shiotsuka et al. (2006)) for 6 h/d, 5 d/wk for 1 wk (total of 5 exposures, 30

h). Actual concentrations were 0, 0.027, 0.1, 0.46, and 1.97 ppm (0, 0.19, 0.7, 3.2, and 13.8 $mg/m^3$, respectively). These rats/group were sacrificed one week after the last exposure and five of these rats/group were allowed to recover during a 6-wk post-exposure period.

No compound-related effects were found for body weights, clinical chemistry, urinalysis, hematology, or organ weights, indicating no evidence of systemic toxicity. Histopathology revealed an epithelial atrophy and/or degeneration in the nasal cavities predominantly in the rostral levels of rats from the three highest exposure levels (0.1, 0.46, 1.97 ppm). Rats exposed at 0.46 and 1.97 ppm showed minimal to moderate graded epithelial lesions as well as turbinate remodeling in the nasal cavities. A borderline (if any) transitional response from adaptation to adversity within the very proximal nasal passage was identified at 0.1 ppm. Irritation-related changes in the larynx, a minimal or slight epithelial metaplasia, coexisting with minimal epithelial alteration and inflammatory infiltrates, were observed at 1.97 ppm. In the lungs of rats at 1.97 ppm enlarged and/or foamy alveolar macrophages, partly with brownish cytoplasm were observed in the absence of inflammatory changes. After 6 wks of recovery, the epithelial atrophy and/or degeneration in the roastral locations of the nasal cavities is still detectable with decreased severity and with signs of epithelial regeneration. The neurodegeneration in rats at the 1.97 ppm group, however, is more pronounced.

The study author determined that, based on pathological findings, the no-observed effect level (NOEL) is 0.027 ppm and exposure to HDI vapor at 0.1 ppm constituted the borderline NOAEL based on effects observed in the upper respiratory tract (typical anterior-posterior gradient of irritation-related injury in the nasal cavities). Furthermore, degeneration of the olfactory epithelium, an adverse effect, was only statistically significantly increased at the two higher exposure concentration 0.46 and 1.97 ppm in the dorsal meatus regions and dorsal nasal septum. The investigators considered the levels of 0.027 and 0.10 ppm of HDI vapor as the NOAEL and LOAEL, respectively.

### *3.2.1.2 Supporting Studies*

#### *3.2.1.2.1 Shiotsuka et al. 2006*

In a 21-d subacute inhalation toxicity study by Shiotsuka et al. (2006, published study based on results from an industrial report, Sangha 1984), groups of 10 male and 10 female Sprague-Dawley (SD) rats were exposed (head only) to 0, 0.005, 0.0175, or 0.150 ppm HDI vapor (mean analytical concentrations) for 5 h/d, 5 d/wk for 3 wks (total of 15 exposures, 75 h). Five rats/sex/group were sacrificed after the last exposure and the remaining animals were sacrificed 2 wks post-exposure**.** No compound-related effects were found for body weights, clinical chemistry, urinalysis, hematology, or organ weights, indicating no evidence of systemic toxicity. The authors mentioned that nasal and ocular irritation were observed, but no details

on the dose at which it occurred or the severity were given. The major compound-related effects included histopathologic changes in the nasal epithelium. These findings were particularly prominent at 0.150 ppm. Varying degrees of concordance between exposure concentration and incidence and/or severity of the histopathologic changes were found. However, effects observed in rats exposed to 0.005 or 0.0175 ppm were restricted to the respiratory tract, i.e., histopathologic changes of the nasal epithelium. The histopathologic changes observed at the lower concentration of 0.005 ppm were considered reversible and not adverse in nature by the investigators. Minimal to slight tissue changes with a tendency toward a return to an orderly pattern was observed in most rats exposed to 0.150 ppm and sacrificed after a 2-wk recovery period. The investigators viewed the histopathologic changes in the nasal epithelium as reparative or adaptive compensatory processes that were not considered adverse in nature, in addition to being reversible. Therefore, the levels of 0.005 and 0.0175 ppm were considered a NOEL and LOEL, respectively, for microscopic changes in the nasal cavity. The LOEL of 0.0175 ppm is considered a NOAEL according to the TCEQ Guidelines (TCEQ 2015a). Furthermore, degeneration of the olfactory epithelium, an adverse effect, was only statistically significantly increased at the highest exposure concentration of 0.150 ppm in the dorsal meatus regions and dorsal nasal septum. The investigators considered the levels of 0.0175 and 0.150 ppm of HDI vapor as the NOAEL and LOAEL, respectively.

### 3.2.1.2.2 Lee et al. (2003)

Lee et al. (2003) exposed male C57BL/6 mice to 360 ppb (2.5 mg/m$^3$) HDI monomer vapor for 3 h and BAL fluid was analyzed 24, 48, and 72 h after exposure. No differences in the numbers of macrophages or neutrophils were observed 24, 48 and 72 h after exposure. No significant differences in BAL fluid protein content was observed between HDI-exposed and unexposed animals 24 and 48 h after exposure (0.090 ± 0.004 mg/ml for unexposed, 0.085 ± 0.009 for HDI 24 h, and 0.087 ± 0.015 for HDI 48 h). Only at 72 h after exposure was a significant increase in BAL fluid protein content observed (0.125 ± 0.02, $p< 0.05$ vs all other groups). The level of 360 ppb was identified as NOAEL for increases in the numbers of macrophages or neutrophils. Although a significant difference in BAL fluid protein content was observed at 72 h after exposure, the investigators concluded that lung injury or inflammation were not observed in mice exposed to 360 ppb (2.5 mg/m$^3$) HDI monomer vapor. Thus, the study authors considered this exposure level as the study NOAEL (or LOEL).

### 3.2.1.2.3 Astroff et al. (2000a)

In a combined reproductive/developmental/neurotoxicity study conducted according to OECD Guideline 422 (Astroff et al. 2000a), male and female SD rats (15/sex/group) were exposed (whole body) to 0, 0.005, 0.053, or 0.299 ppm (0.034, 0.361 or 2.033 mg/m$^3$) HDI vapor (analytical concentrations) 6 h/d, 7 d/wk, during a 14-d pre-mating phase, up to a 14-d mating phase, and during a 21-d gestation phase. Neurobehavioral testing was conducted before exposure, after the pre-mating phase, and before termination. No effects on neurologic parameters (functional observation battery; assessment of motor and locomotor activity), or hematology, clinical chemistry, or organ weights were seen at any dose level. Microscopic alterations in the nasal cavity, primarily epithelial hyperplasia, squamous metaplasia, chronic-active inflammation, and more seriously, degeneration of the olfactory epithelium was observed (dose-response) in both male and female adult animals in the 0.053 and 0.299 ppm exposure groups. Histopathologic lesion severity grades were 1-2 (mild or slight) and 2-3 (mild to moderate), respectively, for animals at 0.053 and 0.299 ppm exposure groups. The level of 0.053 ppm was considered a LOAEL (TCEQ 2015a).

### *3.2.1.3 Reproductive/Developmental Toxicity Studies*

No information is available on the reproductive or developmental effects of HDI in humans. No lesions were found in any of the male or female reproductive organs after rats were exposed to 0.005-0.3 ppm HDI vapor for 5 h/d, 5 d/wk for 3 wks (Shiosuka et al. 2006).

A developmental toxicity study (Astroff et al. 2000b) was conducted with HDI vapor in the rat according to OECD Guideline 414. Inseminated rats were exposed to concentrations of 0, 0.005, 0.052, or 0.308 ppm HDI (analytical concentrations) via inhalation (30 female rats/group, whole-body exposure) from GD 0-19 (total of 20 d of exposure, 480 h). Reproductive, dam, litter, and fetal assessment parameters were evaluated. Maternal histopathological and/or gross lesions were assigned a semiquantitative ranking of severity grade and/or stage. No clinical signs and no changes in body weight gain during gestation were observed in dams. Test compound-related maternal effects were restricted to histopathological findings in the nasal cavity of dams in the 0.308 and 0.052 ppm dose groups. No pathological alterations were noted in the larynx, trachea, or lungs in any dose group. No test compound-related effects were observed on any reproductive parameter, or any embryonic endpoints, including pre/post-implantation loss and resorptions. There were no effects on litter size or the number of fetuses per implantation site and no effects on fetal or placental weights were observed. No test compound-related fetal external, visceral, or skeletal findings were observed. No effect on the fetal or litter incidence of total malformations or variations was observed and there was no difference in the incidence of malformations between males and females. No developmental toxicity was observed up to 0.308 ppm (308 ppb), which is the developmental NOAEL from this study.

## 3.2.2 Mode of Action (MOA) Analysis and Dose Metric

The target organ of HDI toxicity in humans is the respiratory tract, with most exposures resulting from inhaling vapors from HDI or its prepolymers (ATSDR 1998). The MOA for an acute irritation-based POD is likely to be based on the high reactivity of the isocyanate group (DFG 2013). The diamine metabolite of HDI formed by acid hydrolysis, hexamethylene diamine (HDA), could be found in the urine of persons exposed to HDI. The elimination half-life of HDI in the urine was determined as 2.5 h (Tinnerberg et al. 1995, as cited in DFG 2013). Because of hydrolysis, the toxic potential of HDI vapor is directly applicable to its concentration and direct interaction with cellular components at the site of exposure (ATSDR 1998). Thus, exposure concentration of the HDI vapor will be used as the dose metric.

## 3.2.3 Selection of the Key Study, POD, and Critical Effect

Table 11 is a summary of the acute and subacute inhalation and reproductive/developmental studies for HDI vapor.

**Table 11. Summary of Acute and Subacute Inhalation HDI Studies**

| Species (n/sex) | Exposure Concentration | Exposure Duration | NOAEL (ppb) | LOAEL (ppb) | Notes (References) |
|---|---|---|---|---|---|
| C57BL/6 mice (4-6 M/group) | 360 ppb | 3 h | 360 | -- | No differences in the numbers of macrophages or neutrophils were observed (Lee et al. 2003) |
| | | | -- | 360 (LOEL) | Statistically significant increase in BAL fluid protein only at 72 h, but not 24 or 48 h after exposure (Lee et al. 2003) |
| Wistar Rats (10/M/group) | 0, 0.027, 0.1, 0.46, or 1.97 ppm | 6 h/d, 5 d/wk for 1 wk (30 h, 5 total exposures) | 27 (NOEL) | 100 (minimal LOAEL) | Nasal cavity (dorsal medial meatus) irritation (Kopf 2015) |
| SD Rats (10/sex/ group) | 0, 5, 17.5, or 150 ppb | 5 h/d, 5 d/wk for 3 wk (75 h, 15 total exposures) | 17.5 | 150 | Olfactory epithelial degeneration, chronic active inflammation (Shiotsuka et al. 2006) |
| SD Rats (30/F/ group) | 0, 5, 50, or 300 ppb | 6 h/d during a 14-d pre-mating phase, up to a 14-d mating phase, and a 21-d gestation phase | 5 | 50 | Maternal toxicity (microscopic lesions, including chronic inflammation, in the nasal turbinates) (Astroff et al. 2000a) |
| | | GD 0-19 (480 h) | 300 | -- | Reproductive/developmental toxicity not observed (Astroff et al. 2000b) |

Although the Astroff et al. (2000a) study provided the lowest LOAEL and NOAEL for nasal effects, this study had a cumulative exposure of up to 49 d (6 h/d, during a 14-d pre-mating phase, up to a 14-d mating phase, and a 21-d gestation phase), which is less ideal for deriving a 1-h ReV than other studies with less total exposure. The only truly acute study for HDI vapor was the Lee et al. (2003) 3-h study, but this study has a number of concerns associated with it. For example, only a single concentration was tested, resulting in a free-standing NOAEL (while protein leakage in BAL was observed at 72 h, it was not at 24 or 48 h, and the study authors considered 360 ppb as the NOAEL for lung injury and inflammation), and very little detail was given about the vapor exposure because the main purpose of this study was to examine the effects of HDI aerosol. Also, from the subacute and chronic studies, it appears that the target region for HDI vapor effects is the nasal cavity, but the Lee et al. (2003) study only examined lung endpoints that would be more likely adversely affected following aerosol exposure. Therefore, the Lee et al. (2003) study was also not used to derive the acute ReV.

There are 2 subacute inhalation studies with shorter total exposure durations which are appropriate to use as key study. The 21-d NOAEL of 17.5 ppb and the 5-d NOAEL of 27 ppb identified, respectively, from the Shiotsuka et al. (2006) and Kopf (2015) studies. The 5-d NOEL of 27 ppb for nasal cavity irritation based on the Kopf (2015) subacute pilot inhalation male Wistar rat study was used as the POD to develop the acute ReV. While the NOAEL of 17.5 ppb identified from the Shiotsuka et al. (2006) study has lower NOAEL than the NOAEL of 27 ppb identified from the Kopf (2015) study, the total exposure duration in the Shiotsuka et al. (2006) study (5 h/d, 5 d/wk for 3 wk; total of 75 h of exposure) is longer than that in the Kopf study (6 h/d, 5 d/wk for 1 wk, total of 30 h of exposure). Furthermore, the identified critical effect from the Kopf (2015) study (nasal irritation) is less serious than that identified from the Shiotsuka et al. (2006) study (degenerative changes of olfactory epithelium, in addition to chronic active inflammation in the nasal cavity of rats). To select a POD with less serious or severe critical effect is consistent with Section 3.6.1.3 of the TCEQ Guidelines (TCEQ 2015a). Thus, the 5-d NOAEL of 27 ppb based on the Kopf 2015 study was used to derive the acute ReV.

## 3.2.4 Dosimetric Adjustments

### *3.2.4.1 Exposure Duration Adjustments*

The subacute POD of 27 ppb from the Kopf 2015 is associated with exposure for 6 h/d, 5 d/wk for 1 wk. Conservatively, a single 6-h daily exposure will be used for exposure duration adjustment to 1 h. The duration adjustment will use Haber's rule as modified by ten Berge (1986) with an "n" of 3, consistent with Section 4.2.2 of TCEQ (2015a).

$$POD_{ADJ} = C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(27 \text{ ppb})^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 49.06 \text{ ppb}$$

The $POD_{ADJ}$ is therefore 49.06 ppb.

#### *3.2.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure*

The $POD_{ADJ}$ of 49.06 ppb was then adjusted to a $POD_{HEC}$ by a regional gas dose ratio (RGDR). Subacute exposure to HDI vapor caused histopathologic changes in the nasal cavity, which is considered a POE effect, so default dosimetric adjustment from animal-to-human exposure for HDI vapor was conducted as a Category 1 vapor. For a Category 1 vapor, a default dosimetric adjustment factor (DAF) of 1 is used, as recommended by the USEPA (2012). Accordingly, the $POD_{HEC}$ = $POD_{ADJ}$ x default DAF. The resulting $POD_{HEC}$ from the $POD_{ADJ}$ of 49.06 ppb is 49.06 ppb.

### 3.2.5 Adjustments of the $POD_{HEC}$

The NOAEL-based $POD_{HEC}$ of 49.06 ppb for nasal cavity irritation in rats exposed to HDI vapor exposed to HDI vapor was used to derive the acute ReV and $^{acute}$ESL applicable to both HDI and MDI vapors. The following UFs were applied to the $POD_{HEC}$ (Total UF = 30):

- $UF_H$ of 10 for intraspecies variability. A lower $UF_H$ is not supported as no data were identified suggesting that potentially sensitive subpopulations would be similarly sensitive to HDI and/or MDI exposure as the general population;
- $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences.
- $UF_D$ of 1 was used in consideration of the overall database. Several acute or subacute animal studies were conducted with multiple animal species used in inhalation bioassays for HDI and/or MDI vapor. Additionally, acute toxicity studies of PHDI aerosol are available for two species and support the HDI vapor POD. More specifically, the acute mouse LOAEL POD for HDI aerosol (1.3 mg/m$^3$) is very similar to the rat LOAEL for the HDI vapor critical effect (100 ppb or 0.7 mg/m$^3$). Thus, acute/subacute data for HDI vapor and aerosol strongly support the acute POD. Neither short- nor long-term reproductive/developmental studies in rats exposed to HDI vapor have shown developmental or reproductive effects (Sections 3.2.1.3 and 4.2.1.4). For example, while no reproductive/developmental/neurological effects were observed in multiple-day, repeated exposure concentrations up to 299 ppb (Astroff et al. 2000b), respiratory tract effects were observed at ≥ 53 ppb and included those that were more serious in nature (e.g., degeneration of the olfactory epithelium). Respiratory tract effects also appeared to be more sensitive for another reactive diisocyanate aerosol, PMDI. The reactivity of diisocyanates, in conjunction with data

demonstrating numerous respiratory tract effects (including those more severely adverse) in the absence of developmental/reproductive effects at even higher exposure concentrations, mitigates concern about reproductive/developmental effects being more sensitive than respiratory tract effects. These considerations (i.e., acute/subacute HDI vapor studies in two species, acute study results for HDI aerosol), reproduction/developmental study result LOAELs and NOAELs for HDI vapor and PMDI aerosol and their reactivity at the point of exposure) inform and support the acute POD for HDI vapor as conservative such that the acute ReV is expected to be protective against potential reproductive/developmental effects. Thus, the protectiveness of the acute POD for deriving the acute ReV is strongly supported by considerable data. Accordingly, confidence in the database is considered high. The quality of the key rat studies is high.

Acute ReV = $POD_{HEC}$ / ($UF_H$ x $UF_A$ x $UF_D$)
= 49.06 ppb / (10 x 3 x 1)
= 1.635 ppb
= 1.6 ppb or 11 µg/$m^3$ (rounded to two significant figures)

## 3.2.6 Health-Based Acute ReV and $^{acute}$ESL for MDI and HDI, Vapor

The $^{acute}$ESL of 3.3 µg/$m^3$ for HDI vapor is based on the acute ReV of 11 µg/$m^3$ multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 12).

**Table 12. Health-Based Acute ReV and $^{acute}$ESL for MDI and HDI, Vapor**

| Parameter | MDI and HDI Vapor |
|---|---|
| Study | Kopf 2015 |
| Study Quality | High |
| Study Population | Wister male Rats (10/group) |
| Exposure Method | Inhalation to 0.027, 0.1, 0.46, & 1.97 ppm HDI Vapor |
| Exposure Duration | 6 h/d, 5 d/wk for 1 wk |
| Critical Effects | Nasal cavity (dorsal medial meatus) irritation |
| POD | 27 ppb (NOAEL) |
| $POD_{ADJ}$ to 1 h | 49.06 ppb |
| $POD_{HEC}$ | 49.06 ppb |
| Total UFs | 30 |
| *Intraspecies UF* | 10 |
| *Interspecies UF* | 3 |
| *Extrapolation from LOAEL to NOAEL* | N/A |
| *Incomplete Database UF*<br>*Database Confidence* | 1<br>High |
| **Acute ReV [1 h] (HQ = 1)** | **11 µg/m$^3$** |
| **$^{acute}$ESL [1 h] (HQ = 0.3)** | **3.3 µg/m$^3$** |

## *3.3 Welfare-Based Acute ESLs*

### 3.3.1 Odor Perception

HDI vapor has a sharp/pungent odor. DFG (2013) reports that the odor could be perceived at concentrations as low as 35 µg/m$^3$ (5 ppb). However, the odor threshold value did not meet the criteria as described in the TCEQ Approaches to Derive Odor-Based Values (TCEQ 2015b); therefore, no odor-based ESL was developed. The derived acute ReV and ESL for HDI vapor are lower than the odor threshold value of 35 µg/m$^3$ (5 ppb) and are expected to be protective against potential odor nuisance.

### 3.3.2 Vegetation Effects

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

## *3.4 Short-Term ESLs and Values for Air Monitoring Data Evaluations*

### 3.4.1 MDI and HDI Aerosol

The acute evaluation resulted in the derivation of the following values for HDI and MDI aerosols:

- Acute ReV = 27 µg/m$^3$
- $^{acute}$ESL = 8.1 µg/m$^3$

The short-term ESL for air permit reviews for aerosol is the health-based $^{acute}$ESL of 6.9 µg/m$^3$.

### 3.4.2 MDI and HDI Vapor

The acute evaluation resulted in the derivation of the following values for HDI and MDI vapors:

- Acute ReV = 11 µg/m$^3$
- $^{acute}$ESL = 3.3 µg/m$^3$

The short-term ESL for air permit reviews for HDI/MDI vapor is the health-based $^{acute}$ESL of 3.3 µg/m$^3$.

## *3.5 Acute/Subacute Inhalation Observed Adverse Effect Levels (IOAELs)*

### 3.5.1 MDI and HDI Aerosol

The LOAEL of 2.4 mg/m$^3$ for minimal acute pulmonary irritation from the Pauluhn et al. (1999) 150-min study was used as the POD for calculation of an acute inhalation observed adverse

effect level ($^{acute}$IOAEL). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. That is, the LOAEL of 2.4 mg/m$^3$ was adjusted to a $LOAEL_{HEC}$. The calculated $LOAEL_{HEC}$ was then used as the $^{acute}$IOAEL.

For MDI and HDI aerosol, the $LOAEL_{HEC}$ was calculated from the LOAEL multiplied by the RDDR. As described in Section 3.1.4.2, the RDDR of 0.6789 was used to yield a $LOAEL_{HEC}$:

$$LOAEL_{HEC} = LOAEL \times RDDR = 2.4\ mg/m^3 \times 0.6789 = 1.6293\ mg/m^3$$

Effects occurred in some animals and the $^{acute}$IOAEL 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 was used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The $^{acute}$IOAEL level is provided for informational purposes only (TCEQ 2015a). The $^{acute}$IOAEL for MDI and HDI aerosol is:

MDI and HDI aerosol $^{acute}$IOAEL = 1.6 mg/m$^3$ (rounded to 2 significant figures)

The margin of exposure between the $^{acute}$IOAEL (1.6 mg/m$^3$) and the acute ReV (27 µg/m$^3$) for MDI and HDI aerosol is a factor of approximately 59.

### 3.5.2 MDI and HDI Vapor

The 5-d minimal LOAEL of 100 ppb based on a subacute inhalation SD rat study (Kopf 2015) was used as the POD to develop the subacute inhalation observed adverse effect level ($^{subacute}$IOAEL). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. The LOAEL of 100 ppb was adjusted from an animal concentration to a human equivalent concentration ($LOAEL_{HEC}$). The calculated $LOAEL_{HEC}$ is then used as the $^{subacute}$IOAEL.

For MDI and HDI vapor (Category 1 vapor), the $LOAEL_{HEC}$ was calculated from the LOAEL multiplied by a default RGDR of 1 (see Section 3.2.4.2).

$$LOAEL_{HEC} = LOAEL \times RGDR = 100\ ppb \times 1 = 100\ ppb$$

Effects occurred in some animals and the $^{subacute}$IOAEL 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 (≥ 5 d). Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The $^{subacute}$IOAEL level is provided for informational purposes only (TCEQ 2015a). The $^{subacute}$IOAEL for MDI and HDI vapor is:

MDI and HDI vapor $^{subacute}$IOAEL = 100 ppb

The margin of exposure between the $^{subacute}$IOAEL (100 ppb or 690 µg/m$^3$) and the acute ReV (1.6 ppb or 11 µg/m$^3$) for MDI and HDI vapor is a factor of ~60.

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential of MDI and HDI, Aerosol*

Human studies have suggested that chronic exposure to MDI and HDI aerosol may cause chronic lung problems. Respiratory effects of MDI and HDI have been reported in several human case reports or epidemiologic studies; however, these studies have difficulties (e.g., inaccurate exposure data, confounding factors) in relating a specific effect in humans to exposure in the workplace. Chronic effects of occupational exposure studies and effects on nasal tissue, the respiratory tract, and the lungs were reported in USEPA (1998), DFG (1997, 2008, 2013), IPCS (2000), OEHHA (2016), and ATSDR (2018) documents.

## 4.1.1 Key and Supporting Studies

### *4.1.1.1 Key Studies*

#### 4.1.1.1.1 MDI Key Studies

##### *4.1.1.1.1.1 Reuzel et al. 1994b*

In a 2-year (yr) chronic inhalation study by Reuzel et al. (1994b), groups of Wistar rats (60/sex/group) were exposed whole body to 0, 0.2, 1.0, or 6.0 mg/m$^3$ (target concentrations) of 47% MDI/53% PMDI respirable aerosol (93.5% < 4.2 µm) for 6 h/d, 5 d/wk for up to 24 months. The corresponding measured concentrations (mean ± SD) were 0, 0.19 ± 0.05, 0.98 ± 0.11, or 6.03 ± 0.54 mg/m$^3$, respectively. In addition, other groups of 10/sex/group received the same treatment for 12 months. The MMAD ± GSD corresponding to the exposure levels were 0, 0.68 ± 2.93, 0.70 ± 2.46, and 0.74 ± 2.31 µm, respectively. There were no adverse effects on general health, survival, body weight, hematological, or clinical chemistry parameters. Statistically significant increases in lung weight and histopathological changes in the nasal cavity, lungs, and mediastinal lymph nodes were found in the following endpoints in the 12- and 24-month groups:

In the 12-month satellite study:

- Absolute and relative lung weights were increased in both males and females exposed to 6.03 mg/m$^3$;
- Minimal-to-moderate disarrangement of the olfactory epithelium was observed in males at 6.03 mg/m$^3$;
- Accumulation of macrophages with yellow pigment was seen in the lungs of both sexes at 0.98 and 6.03 mg/m$^3$;

- Minimal-to-moderate localized fibrosis was significant in males exposed to 6.03 mg/m$^3$ and in females at 0.98 and 6.03 mg/m$^3$; Alveolar duct epithelialization increased in males and females exposed to 6.03 mg/m$^3$; and

Interstitial pneumonitis increased in males at 0.98 and 6.03 mg/m$^3$. In the 24-month study:

- Absolute and relative lung weights were increased in both males and females exposed to 6.03 mg/m$^3$;
- Alveolar duct epithelialization as well as macrophage accumulation with yellow pigment in the lungs occurred in both males and females at the 0.98 and 6.03 mg/m$^3$ exposure levels;
- Localized fibrosis of lung tissues surrounding the macrophage accumulations occurred at 0.98 and 6.03 mg/m$^3$ in both sexes;
- Olfactory epithelial degeneration was elevated significantly in males and females at 6.03 mg/m$^3$;
- Hyperplasia of Bowman's glands was found only in males at 0.98 and 6.03 mg/m$^3$;
- Basal cell hyperplasia of the nasal olfactory epithelium was elevated significantly in males at 0.98 and 6.03 mg/m$^3$ and in females at 6.03 mg/m$^3$; and
- Lung adenomas were seen in 6 males and 2 females exposed to 6.03 mg/m$^3$.

Tables 13 and 14 contain data on histopathological changes that were statistically significant in the 0.98 and 6.03 mg/m$^3$ exposure groups with an adequate dose-response relationship in the 2-yr study.

**Table 13. Incidences of Histological Changes in the Lungs from Reuzel et al. (1994b)**

| PMDI Aerosol Concentration | 0 mg/m³ | 0.19 mg/m³ | 0.98 mg/m³ | 6.03 mg/m³ |
|---|---|---|---|---|
| Males (#) | (60) | (60) | (60) | (60) |
| Macrophage Accumulation | 0 | 3 | 21** | 60** |
| Alveolar Duct Epithelialization | 1 | 0 | 8* | 54** |
| Localized Fibrosis | 1 | 0 | 9* | 44** |
| Females (#) | (59) | (60) | (60) | (59) |
| Macrophage Accumulation | 0 | 1 | 23** | 59** |
| Alveolar Duct Epithelialization | 0 | 0 | 8* | 57** |
| Localized Fibrosis | 0 | 0 | 4 | 48** |
| Combined (#) | (119) | (120) | (120) | (119) |
| Macrophage Accumulation | 0 | 4 | 44 | 119 |
| Alveolar Duct Epithelialization | 1 | 0 | 16 | 111 |
| Localized Fibrosis | 1 | 0 | 13 | 92 |

Note: total number of animals exposed are provided in parenthesis. *P<0.05; **P<0.01

**Table 14. Incidences of Histological Changes in the Nasal Cavity from Reuzel et al. (1994b)**

| PMDI Aerosol Concentration | 0 mg/m³ | 0.19 mg/m³ | 0.98 mg/m³ | 6.03 mg/m³ |
|---|---|---|---|---|
| Males (#) | (60) | (60) | (60) | (60) |
| Bowman's gland hyperplasia | 0 | 2 | 9** | 17** |
| Basal cell hyperplasia | 14 | 13 | 26* | 32** |
| Olfactory epithelial degeneration | 6 | 9 | 15 | 25* |
| Females (#) | (60) | (60) | (60) | (59) |
| Bowman's gland hyperplasia | 2 | 6 | 8 | 8 |
| Basal cell hyperplasia | 4 | 8 | 8 | 49** |
| Olfactory epithelial degeneration | 8 | 16 | 10 | 20* |
| Combined (#) | (120) | (120) | (120) | (119) |
| Bowman's gland hyperplasia | 2 | 8 | 17 | 25 |
| Basal cell hyperplasia | 18 | 21 | 34 | 81 |
| Olfactory epithelial degeneration | 14 | 25 | 25 | 45 |

Note: total number of animals exposed are provided in parenthesis. *P<0.05; **P<0.01

In summary, this study showed that the effect of chronic exposure of rats to PMDI aerosol was confined to the respiratory tract. Exposure to 0.98 mg/m$^3$ resulted in significant increases in the incidence of basal cell hyperplasia, Bowman's gland hyperplasia in the nasal cavity, mild to moderate localized fibrosis in the lungs, and alveolar duct epithelialization. The incidence of olfactory degeneration was significant only in the 6.03 mg/m$^3$ group. The 2-yr study identified a NOAEL and LOAEL of 0.19 and 0.98 mg/m$^3$, respectively, for histopathological changes in the lungs and nasal cavity.

#### *4.1.1.1.1.2 Hoymann et al. (1995, as cited in Feron et al. 2001; OEHHA 2016) Study*

In an unpublished study conducted by Hoymann et al. (1995, as cited in OEHHA 2016), groups of 80 female Wistar rats were exposed to 0, 0.23 ± 0.06, 0.70 ± 0.17, or 2.05 ± 0.37 mg/m$^3$ monomeric MDI aerosols (analytical concentrations) for 17 h/d, 5 d/wk for approximately 2 yrs. The MMAD ± GSD corresponding to the exposure levels were 0, 1.03 ± 0.17, 1.03 ± 0.18, and 1.06 ± 0.23 µm, respectively. Lung function was assessed after 6, 12, 17, and 20 months, with histological evaluations after 12 and 24 months. Significant increases in absolute and relative lung weights were observed only at 2.05 mg/m$^3$. In the nasal cavity, no difference was observed in the incidence of basal cell hyperplasia between controls and any exposure group (USEPA 2002). Examination of BAL fluid showed an inflammatory reaction, with increased numbers of lymphocytes, at all time points at the highest dose. At all time points, the highest exposure (2.05 mg/m$^3$) caused a significant decrease in maximum mid-expiratory flow (MMEF), and forced expiratory flows (FEF) at 10, 25, and 50%, but not 75% of forced vital capacity. A number of histological alterations were observed to be statistically significant in the lungs; the incidence and severity of the lesions appeared to be concentration related:

- Peribronchiolar and interstitial fibrosis were observed in all exposure groups;
- Alveolar and bronchiolar hyperplasia were observed in the 0.70 and 2.05 mg/m$^3$ exposure groups; and
- Alveolar cell hyperplasia was observed in the 0.70 and 2.05 mg/m$^3$ exposure groups.

Table 15 is a summary of incidences of pulmonary lesions observed in female rats in this Hoymann et al. (1995) study reported in OEHHA (2016). Interpretation of the results of this study are impeded by the high rate of mortality (94-97%, including the control group) from causes unrelated to MDI exposure.

**Table 15. Incidence of Pulmonary Lesions in Female Rats Exposed to Monomeric MDI from Hoymann et al. (1995)**

| PMDI Aerosol Concentration | 0 mg/m$^3$ | 0.23 mg/m$^3$ | 0.70 mg/m$^3$ | 2.05 mg/m$^3$ |
|---|---|---|---|---|
| Number of Lungs Examined | 80 | 80 | 80 | 80 |
| Peribronchiolar and Interstitial Fibrosis | 4 | 51** | 73** | 77** |
| Alveolar and Bronchiolar Hyperplasia | 3 | 6 | 14* | 41** |
| Alveolar Cell Hyperplasia | 2 | 8 | 12* | 21** |

Source: CalEPA OEHHA (2016); * p<0.05, ** P<0.001

A LOAEL of 0.23 mg/m$^3$ for histopathologic effects in the lungs was identified from this study. While this LOAEL is less than the LOAEL from the Reuzel et al. (1994b) key study, after duration adjustment the adjusted LOAEL (0.12 mg/m$^3$) would be similar to the adjusted LOAEL (0.175 mg/m$^3$) from the Reuzel et al. (1994b) study, which also provides a NOAEL. The study discussed below (Feron et al. 2001) further evaluated results from both Hoymann et al. (1995) and Reuzel et al. (1994b).

#### *4.1.1.1.1.3 Feron et al. (2001) Study*

Feron et al. (2001) reanalyzed bioassays from both the TNO (Reuzel et al. 1994b) and Fraunhofer (Hoymann et al. 1995) chronic studies. In this study, an in-depth review of lesions in the lungs of female rats (e.g., re-examination of the original lung slides) was conducted by an independent reviewing pathologist. This re-evaluation of the lung findings was confined to female rats as the Hoymann et al. (1995) study only used female rats. The investigators indicated that results from the Reuzel et al. (1994b) study showed a similar pattern of pathologic findings for male rats as well. Histopathologic findings were then combined to give an overall dose-response curve for both studies. The range of total inhalation exposure concentrations (taking into consideration exposure duration) to PMDI or monomeric MDI was calculated as 559, 1972, 2881, 6001, 17,575 and 17,728 mg/m$^3$, respectively, for the exposure regimes of 0.19, 0.23, 0.7, 0.98, 6.03, and 2.05 mg/m$^3$. Table 16 summarizes the incidence of major microscopic findings in the lungs of female rats exposed to monomeric or polymeric MDI.

**Table 16. Incidence of Major Microscopic Findings in the Lungs of Female Rats Exposed to MDI/PMDI from Feron et al. (2001)**

| | TNO Study (Reuzel et al. 1994b) | | | | Fraunhofer Study (Hoymann et al. 1995) | | | |
|---|---|---|---|---|---|---|---|---|
| Exposure Concentration (mg/m$^3$) | 0 | 0.19 | 0.98 | 6.03 | 0 | 0.23 | 0.7 | 2.05 |
| Total Dose (mg/m$^3$) | 0 | 559 | 2,881 | 17,728 | 0 | 1,972 | 6,001 | 17,575 |
| No. of Animals/Group | 60 | 60 | 60 | 60 | 80 | 80 | 80 | 80 |
| No. of Lungs Examined | 59 | 60 | 60 | 59 | 80 | 80 | 80 | 80 |
| Bronchiolo-alveolar Hyperplasia | 11 | 10 | 25 | 59 | 8 | 10 | 27 | 53 |
| Interstitial Fibrosis | 2 | 2 | 19 | 59 | 13 | 63 | 77 | 79 |
| Bronchiolo-alveolar Adenoma | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |

The results of this reanalysis showed that major pulmonary effects including increases in lung weights, bronchiolo-alveolar adenomas and hyperplasia, and interstitial fibrosis occurred consistently in both MDI aerosol exposure studies. A dose-response relationship was clearly shown in each study as well as with the combined data for inflammatory and other non-neoplastic pulmonary changes. The lowest dose examined (559 mg/m$^3$ - exposure regime of 0.19 mg/m$^3$ for the Reuzel et al. (1994b) study) was regarded by Feron et al. (2001) as a NOAEL for both studies.

### 4.1.1.1.2 HDI Key Study – Pauluhn and Mohr (2001)

In a 13-wk subchronic inhalation study by Pauluhn and Mohr (2001), groups of 10 Wistar rats/sex/group were exposed nose-only to 1,6-hexamethylene diisocyanate isocyanurate (HDI-IC) or - biuret (HDI-BT) for 6 h/d, 5 d/wk for 13 wks. The mean analytical concentrations (± standard deviation) of HDI-IC were 0, 0.5 ± 0.2, 3.3 ± 0.9, and 26.4 ± 5.8 mg /m$^3$ with MMAD ± GSD of 1.5 ± 1.4, 1.4 ± 1.3, and 1.5 ± 1.6 µm, respectively, for the low, intermediate, and high exposure groups. The mean analytical concentrations (± standard deviation) of HDI-BT were 0, 0.4 ± 0.1, 3.4 ± 2.1, and 21.0 ± 5.1 mg/m$^3$ with MMAD ± GSD of 1.4 ± 1.3, 1.5 ± 1.4, and 3.3 ± 1.6 µm for the low, intermediate, and high exposure groups, respectively. All experiments and procedures described were performed in compliance with the OECD GLP standards. Following exposure, compound-related effects were found only in the high-level exposure groups of HDI-IC or HDI-BT and included mild respiratory distress, marginally decreased body weights, and increased lung weights. Increases of wet lung weights of exsanguinated male rats in the HDI-IC and HDI-BT high-level exposure groups were slightly higher than those in the low- and intermediate-level exposed groups but were statistically significant. In female rats, wet lung weights were significantly increased only in the HDI-IC high-level exposure group. Relative lung

weights of both male and female rats were significantly increased in the HDI-IC and HDI-BT high-level as well as in the intermediate HDI-BT exposure groups. The only hematological effect observed was a mild but significant increase of leukocytes in rats in the high-level exposure groups of HDI-BT and HDI-IC without associated changes in differential blood counts. Pulmonary function testing revealed minimal changes from HDI exposure indicative of increases in functional residual capacity and total lung capacity but without evidence of increased bronchial hyperreactivity to acetylcholine aerosol.

Histopathology demonstrated statistically significant increased incidences of proliferative responses in the bronchiolo-alveolar region, including increased influx of AM and septal round-cell infiltrations with fibrosis in both of the HDI-BT and HDI-IC high-level exposure groups. No adverse histopathologic effects were observed in the low and intermediate exposure groups (Table 17). Accordingly. the NOAELs for pulmonary irritation were 3.3 and 3.4 mg/m$^3$, respectively, for HDI-IC and HDI-BT exposure. The subchronic NOAELs were similar to the 21-d NOAEL of 3.7-4.3 mg/m$^3$ from the dose range-finding study by the same investigators (Section 3.1.1.2.2.3). Additionally, the subchronic LOAEL (26.4 mg/m$^3$) was higher than the 21-d LOAELs (14.7-17.5 mg/m$^3$) due to dose selection. The subchronic NOAEL of 3.3 mg/m$^3$ was used as a candidate POD to derive a chronic ReV and ESL for polymeric HDI.

**Table 17. Incidence of Exposure-related Histopathologic Lesions After 13-wk Exposure from Pauluhn and Mohr (2001)**

| Exposure Group | Control | Low | Intermediate | High |
|---|---|---|---|---|
| HDI-BT (# of lungs) | (20) | (20) | (20) | (20) |
| Increased number of AM | 1 | 1 | 0 | 6* |
| Thickening of septa | 0 | 0 | 1 | 7* |
| Interstitial fibrosis | 0 | 1 | 1 | 4 |
| Bronchiolo-alveolar proliferation | 0 | 1 | 0 | 16** |
| HDI-IC (# of lungs) | (20) | (20) | (20) | (20) |
| Increased number of AM | 0 | 0 | 1 | 20** |
| Thickening of septa | 0 | 0 | 1 | 6** |
| Interstitial fibrosis | 0 | 0 | 1 | 6** |
| Bronchiolo-alveolar proliferation | 1 | 0 | 1 | 20** |

* P<0.05; ** P<0.01

### *4.1.1.2 Supporting Studies*

#### 4.1.1.2.1 MDI Supporting Studies

Effects of MDI/PMDI aerosol on lung function were assessed by *Deutsche Forschungsgemeinschaft* (DFG 1997) based on the results of nine occupational studies (Cavelier et al. 1977; Pham et al. 1978, 1986, 1988; Martin et al. 1982; Diller & Herbert 1982; Musk et al. 1982; Gee and Morgan 1985; and Sulotto et al. 1990) (refers to Section 2.2 of the 1997 DFG documentation). The DFG stated that there were many limitations in these studies, e.g., involvement of confounding factors (cigarette smoking, co-exposure to toluene diisocyanate (TDI) and/or other chemicals, and inaccurate exposure data). In these studies, a significant impairment of lung spirometry values was observed in the collective group exposed to PMDI concentrations up to 0.9 mg/m$^3$. No significant changes in lung spirometry were found at concentrations below 0.2 mg/m$^3$. Significantly more frequent respiratory symptoms were observed at concentrations between 0.1 and 0.2 mg/m$^3$, but no increased symptoms were observed at 0.05 mg/m$^3$ or less. The TCEQ considers the level of 0.05 mg/m$^3$ as a NOAEL for respiratory symptoms from these results. The NOAEL (0.05 mg/m$^3$) was consistent with the BMDL/$POD_{HEC}$ of 0.05536 mg/m$^3$ for bronchioloalveolar hyperplasia in female rats from the Feron et al. (2001) study.

Reuzel et al. (1994a) conducted a subchronic study in which groups of male and female 6 wk-old Wistar rats (15/sex/group) were exposed to 0.35, 1.4, or 7.2 mg/m$^3$ (mean analytical concentrations) PMDI aerosol (95% < 5 µm with the major part having particle size between 0.4 to 2.0 µm) for 6 h/d, 5 d/wk, for 13 wks. The study revealed transient growth retardation and a slightly increased number of pulmonary AM occasionally accompanied by increased numbers of mononuclear cells and fibroblasts in alveolar septa only at 7.2 mg/m$^3$. In a second 13-wk study, the study investigators exposed 6 wk-old rats (30 rats/sex/group) to mean analytical PMDI aerosol concentrations of 0, 4.07, 8.43, or 12.25 mg/m$^3$ (95% < 5 µm) for 6 h/d, 5 d/wk, for 13 wks with a 4-wk recovery period. Exposure to 12.25 mg/m$^3$ induced mortality (11/30 males and 4/30 females died or were euthanized in extremis during the first 7 wks of the study, specific cause of death not mentioned), growth retardation, severe respiratory distress, increased lung weights, degeneration and hyperplasia of the nasal epithelium, accumulation of macrophages in the lungs and mediastinal lymph nodes, and focal inflammatory changes in the lungs. Rats exposed to 8.43 mg/m$^3$ showed respiratory distress, lower body weights in males, increased lung weights, and much less severe histopathological changes in the respiratory tract and mediastinal lymph nodes compared to those observed in rats exposed to 12.25 mg/m$^3$. These studies demonstrated clear adverse pulmonary and nasal effects at 8.43 mg/m$^3$, including some more serious in nature (e.g., respiratory distress). At PMDI concentrations of 4.07 mg/m$^3$ relatively minor but statistically significant histopathological changes in the respiratory tract

were also observed. A NOAEL and a LOAEL of 1.4 and 4.07 mg/m$^3$, respectively, were identified from these two 13-wk studies.

#### 4.1.1.2.2 HDI Supporting Studies

No additional studies were located regarding chronic effects following HDI aerosol exposure.

### *4.1.1.3 Reproductive and Developmental Studies*

#### 4.1.1.3.1 MDI Reproductive and Developmental Studies

No information was identified regarding reproductive/developmental effects in humans following inhalation exposure to MDI. A 2-yr study in male and female rats did not find histological alterations in the gonads at 6.0 mg/m$^3$ PMDI (Reuzel et al. 1994b). The results from other reproductive and developmental toxicity studies were discussed in Section 3.1.1.3.

#### 4.1.1.3.2 HDI Reproductive and Developmental Studies

No information was located regarding reproductive/developmental effects in humans or regarding developmental effects in animals following inhalation exposure to HDI aerosol.

## 4.1.2 Mode-of-Action (MOA) Analysis and Dose Metric

As described in Section 3.2.2, the MOA for a lung irritation-based POD is likely to be based on the high reactivity of the isocyanate group. The MOA for pulmonary inflammation and bronchoalveolar hyperplasia is likely related to the high reactivity of the isocyanate group (DFG 2013, ATSDR 1998). Once absorbed, MDI and HDI appear to be predominantly conjugated to proteins. Because of hydrolysis, the toxic potential of MDI and HDI is directly applicable to its concentration and direct interaction with cellular components at the site of exposure (ATSDR 1998). The direct pulmonary irritation of MDI and HDI aerosol is at the site of initial deposition of aerosol (Pauluhn and Mohr 2001). Thus, MDI/HDI aerosol exposure concentration will be used as the dose metric. MOA information indicates that the adverse health effects observed in rats are relevant for humans.

## 4.1.3 Selection of the Key Study, POD, and Critical Effect

### *4.1.3.1 Selection of the MDI Key Study*

Numerous histopathological lesions in the lungs and nasal cavities of rats were observed following PMDI exposure (Reuzel et al. 1994b, Hoymann et al. 1995, Feron et al. 2001). The TCEQ selected several of the endpoints identified in Reuzel et al. (1994b) and Feron et al. (2001) that were statistically significant at both the mid and high-level concentrations. The Reuzel et al. 1994b 2-yr study identified a NOAEL and LOAEL of 0.19 and 0.98 mg/m3 respectively for histopathological changes in the lungs and nasal cavity. Data from the Hoymann et al. (1995)

study were not used due to the high incidence of unrelated mortality at 2 yrs in all groups (94-97%), including the control group. In the Reuzel et al. (1994b) study, on the other hand, mortality at 2 yrs amounted to 30, 28, 20 and 16% for the control, low-, mid- and high-concentration groups, respectively (Feron et al. 2001). Furthermore, only a LOAEL of 0.23 mg/m3 but not NOAEL was identified from the Hoymann et al. (1995) study. While this LOAEL is less than the LOAEL from the Reuzel et al. (1994b) key study, after duration adjustment the adjusted LOAEL (0.12 mg/m3) would be similar to the adjusted LOAEL (0.175 mg/m3) from the Reuzel et al. (1994b) study, which also provides a NOAEL. Thus, the NOAEL from the Reuzel et al. (1994b) MDI aerosol rat study (0.19 mg/m3) was selected as a candidate POD to derive a chronic ReV and ESL for both PMDI and PHDI. The critical effect was histopathological changes in the lungs and nasal cavity.

#### *4.1.3.2 Selection of the HDI Key Study*

The subchronic NOAEL of 3.3 mg/m$^3$ for increased lung weights and histopathological changes in the lungs identified from the Pauluhn and Mohr (2001) study was considered for use as the POD to derive a chronic ReV and ESL for polymeric HDI. The critical effect was histopathological changes in the lungs.

#### *4.1.3.3 Selection of the Overall Key Study*

The Reuzel et al. (1994b) MDI aerosol rat study, in lieu of the Pauluhn and Mohr (2001) HDI aerosol rat study, was selected as the key study for derivation of the chronic ReV and ESL for MDI and HDI aerosols for several reasons, primarily:

- Reuzel et al. (1994b) was a chronic 2-yr study while the Pauluhn and Mohr (2001) study was only a 13-wk subchronic study.
- The Reuzel et al. (1994b) study also used three times as many animals per exposure concentration (i.e., 60 female rats/exposure concentration versus 20 male/female rats combined/exposure concentration).
- Moreover, the Reuzel et al. (1994b) chronic study demonstrated effects at much lower exposure concentrations (not particularly surprising given the appreciable differences in exposure duration and number of animals/exposure group) and use of more sensitive adverse effects is generally preferred for toxicity factor derivation (TCEQ 2015a).
- Consequently, candidate $POD_{HEC}$ values based on effects observed in Reuzel et al. (1994b) are lower, for example:
    - The RDDRs for the effects in the Reuzel et al. (1994b) and Pauluhn and Mohr (2001) studies are 1.4351 (see Table 20 below) and 1.0639 (see Appendix 2.2 and 3.2), respectively. These RDDRs result in $POD_{HEC}$ values of 0.05536 and 0.6212 mg/m$^3$, respectively, for effects observed in the Reuzel et al. (1994b) and Pauluhn and Mohr (2001) studies.

- The $POD_{HEC}$ (0.05536 mg/m$^3$) corresponding to the $BMCL_{10}$ (0.216 mg/m$^3$) for bronchiolo-alveolar hyperplasia in Reuzel et al. (1994b; see Section 4.1.4 below) is 11 times lower than the $POD_{HEC}$ (0.6212 mg/m$^3$) corresponding to the NOAEL (3.3 mg/m$^3$) for respiratory effects from the Pauluhn and Mohr (2001) study.
- The consideration of LOAEL-like values for identification of critical effect(s) demonstrates an even bigger difference, with the $POD_{HEC}$ (0.1691 mg/m$^3$) corresponding to the $BMC_{10}$ (0.66 mg/m$^3$) for bronchiolo-alveolar hyperplasia being ≈30-fold lower than the $POD_{HEC}$ (5 mg/m$^3$) corresponding to the subchronic LOAEL (26.4 mg/m$^3$) for respiratory effects from the Pauluhn and Mohr (2001) study.

- Finally, use of a chronic study alleviates an area of uncertainty and the need to account for it through use of an additional uncertainty factor ($UF_L$), thereby appreciably reducing the overall uncertainty associated with the toxicity factor.

Thus, the Reuzel et al. (1994b) chronic MDI aerosol study was selected as the key study and a $POD_{HEC}$ based on effects demonstrated in this study will ultimately be used to derive a chronic ReV and ESL applicable to both MDI and HDI aerosols.

## 4.1.4 BMC Modeling, Dosimetric Adjustments, and Selection of the Critical Effect

### *4.1.4.1 Benchmark Concentration (BMC) Modeling*

The TCEQ performed Benchmark Concentration (BMC) modeling using USEPA Benchmark Dose (BMD) software (version 2.7) for the Reuzel et al. (1994b) data from: (1) Table 13 (lung lesions) and Table 14 (nasal lesions); and from (2) Table 15, which are Reuzel et al. (1994b) data from the Feron et al. (2001) study reanalysis. Data from the Hoymann et al. (1995) study were not used due to the high incidence of unrelated mortality. Data were used to predict 95% lower confidence limits on the BMCs using dichotomous models. A default benchmark response (BMR) of 10% was selected as an effect threshold ($BMC_{10}$ and $BMCL_{10}$). All the available dichotomous models were run (Appendix 5), and the best fit models are listed in Table 18.

**Table 18. BMC Modeling Results for Histological Changes in the Nasal Cavity and Lungs of Rats Following PMDI exposure**

| Endpoint | Sex | Model | p value | AIC | $BMC_{10}$ | $BMCL_{10}$ | Reason |
|---|---|---|---|---|---|---|---|
| **Reuzel et al. (1994b)** | | | | | | | |
| Macrophage accumulation in the lung | Male | Multistage 2° | 0.997 | 105.53 | 0.350 | 0.217 | Lowest AIC |
| | Female | Multistage 2° | 1 | 92.059 | 0.458 | 0.303 | Lowest AIC |
| | Combined | Multistage 2° | 1 | 196.79 | 0.408 | 0.281 | Lowest AIC |
| Alveolar duct epithelialization | Male | LogProbit | 0.310 | 103.75 | 0.890 | 0.660 | Lowest AIC |
| | Female | LogProbit | 0.998 | 68.600 | 0.883 | 0.693 | Lowest AIC |
| | Combined | LogProbit | 0.308 | 171.89 | 0.884 | 0.732 | Lowest AIC |
| Localized Fibrosis | Male | LogProbit | 0.263 | 138.37 | 0.829 | 0.563 | Lowest AIC |
| | Female | LogProbit | 0.996 | 90.167 | 1.16 | 0.852 | Lowest AIC/BMCL |
| | Combined | LogProbit | 0.288 | 228.97 | 0.974 | 0.766 | Lowest AIC/BMCL |
| Bowman's gland hyperplasia | Male | LogProbit | 0.759 | 144.34 | 0.661 | 0.239 | Lowest AIC/BMCL |
| | Female | LogLogistic | 0.188 | 158.15 | 8.31 | 2.98 | Lowest AIC/BMCL |
| | Combined | Dichotomous-Hill* | 0.899 | 305.41 | 0.560 | 0.331 | Lowest AIC |
| Basal cell hyperplasia | Male | Probit | 0.132 | 300.88 | 0.879 | 0.485 | Lowest AIC |
| | Female | Logistic | 0.501 | 182.66 | 1.27 | 1.03 | Lowest AIC |
| | Combined | Gamma | 0.983 | 508.91 | 0.645 | 0.520 | Lowest AIC |
| Olfactory epithelial degeneration | Male | LogLogistic | 0.475 | 244.19 | 1.19 | 0.702 | Lowest AIC |
| | Female | Multistage 3° | 0.151 | 254.03 | 4.83 | 1.68 | Lowest AIC |
| | Combined | LogLogistic | 0.223 | 496.95 | 1.82 | 1.17 | Lowest AIC |
| **Feron et al. (2001)** | | | | | | | |
| Bronchiolo-alveolar hyperplasia | Female | Multistage 3° | 0.952 | 196.43 | 0.660 | 0.216 | Lowest AIC/BMCL |
| Interstitial fibrosis | Female | Multistage 3° | 0.996 | 113.93 | 0.658 | 0.314 | Lowest AIC/BMCL |

*Model contained an error message, "Warning: BMDL computation is at best imprecise for these data"

### *4.1.4.2 Exposure Duration Adjustments*

The effects of PMDI aerosol are assumed to be concentration- and duration-dependent. Each of the PODs (i.e., each $BMCL_{10}$) was adjusted for intermittent exposure (6 h/d, 5 d/wk). The adjustment from a discontinuous to a continuous exposure duration (TCEQ 2015a) was conducted as follows:

$$POD_{ADJ}\ (BMCL_{ADJ}) = POD\ (BMCL_{10}) \times (D/24\ h) \times (F/7\ d)$$

where:

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

### *4.1.4.3 Default Dosimetric Adjustments from Animal-to-Human Exposure*

Default dosimetric adjustments from animal-to-human exposure were conducted to calculate the $POD_{HEC}$ for the potential critical endpoints. In the key study, an aerosol of PMDI was used. The Long-Evans Asymmetric model was chosen from the available rat models. Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions. According to Reuzel et al. (1994b), the average MMAD of PMDI used in their study was 0.68 μm with an average GSD of 2.93, and the particle density was 1.23 $g/cm^3$. The chemical concentration was the NOAEL of 0.19 $mg/m^3$. Depending on the potential critical effect, the target region was either the extrathoracic (ET) region or the tracheobronchial and pulmonary regions (TB/PU).

Male and female body weights were calculated using time-weighted averages from the 0.2 $mg/m^3$ exposure group. Minute volume, breathing frequency, and tidal volumes were calculated using the time-weighted average body weight. The values for the combined animals were calculated by taking the averages of the male and female data. All remaining values used were default (Table 19).

**Table 19. Calculated Rat Body Weights, Minute Volumes, Breathing Frequencies, and Tidal Volumes**

| Sex | Body Weight (g) | Minute Volume (ml/min) | Breathing Frequency (Breaths/min; default) | Tidal Volume (ml) |
|---|---|---|---|---|
| Male | 523 | 334.16 | 102 | 3.28 |
| Female | 301.5 | 209.64 | 102 | 2.06 |
| Combined | 412.25 | 271.03 | 102 | 2.66 |

Once the total particle distribution was determined (Appendix 2), the RDDR was calculated as follows:

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

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD ($POD_{HEC}$) (Table 20).

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

**Table 20. Endpoints and $POD_{HEC}$ Values for Histological Changes in the Nasal Cavity and Lungs Following PMDI Exposure**

| Endpoint | Sex | $BMCL_{10}$ ($mg/m^3$) | $POD_{ADJ}$ ($mg/m^3$) | Region | BW (kg) | VE (ml/min) | RDDR | $POD_{HEC}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|
| **Reuzel et al. (1994b)** | | | | | | | | |
| Macrophage accumulation in the lung | Male | 0.217 | 0.039 | TB/PU | 0.523 | 334.16 | 2.5026 | 0.09698 |
| | Female | 0.303 | 0.054 | TB/PU | 0.302 | 209.64 | 1.4351 | 0.07765 |
| | Combined | 0.281 | 0.050 | TB/PU | 0.412 | 271.03 | 2.0224 | 0.10148 |
| Alveolar duct epithelialization | Male | 0.660 | 0.118 | TB/PU | 0.523 | 334.16 | 2.5026 | 0.29496 |
| | Female | 0.693 | 0.124 | TB/PU | 0.302 | 209.64 | 1.4351 | 0.1776 |
| | Combined | 0.732 | 0.131 | TB/PU | 0.412 | 271.03 | 2.0224 | 0.26436 |
| Localized Fibrosis | Male | 0.563 | 0.101 | TB/PU | 0.523 | 334.16 | 2.5026 | 0.25161 |
| | Female | 0.852 | 0.152 | TB/PU | 0.302 | 209.64 | 1.4351 | 0.21835 |
| | Combined | 0.766 | 0.137 | TB/PU | 0.412 | 271.03 | 2.0224 | 0.27664 |
| Bowman's gland hyperplasia | Male | 0.239 | 0.043 | ET | 0.523 | 334.16 | 0.4706 | 0.02008 |
| | Female | 2.98 | 0.532 | ET | 0.302 | 209.64 | 0.2193 | 0.11672 |
| | Combined | 0.331 | 0.059 | ET | 0.412 | 271.03 | 0.3378 | 0.01996 |
| Basal cell hyperplasia | Male | 0.485 | 0.087 | ET | 0.523 | 334.16 | 0.4706 | 0.04076 |
| | Female | 1.03 | 0.184 | ET | 0.302 | 209.64 | 0.2193 | 0.04034 |
| | Combined | 0.52 | 0.093 | ET | 0.412 | 271.03 | 0.3378 | 0.03136 |
| Olfactory epithelial degeneration | Male | 0.702 | 0.125 | ET | 0.523 | 334.16 | 0.4706 | 0.05899 |
| | Female | 1.68 | 0.300 | ET | 0.302 | 209.64 | 0.2193 | 0.0658 |
| | Combined | 1.17 | 0.209 | ET | 0.412 | 271.03 | 0.3378 | 0.07057 |
| **Feron et al. (2001)** | | | | | | | | |
| Bronchiolo-alveolar hyperplasia | Female | 0.216 | 0.039 | TB/PU | 0.302 | 209.64 | 1.4351 | 0.05536 |
| Interstitial fibrosis | Female | 0.314 | 0.056 | TB/PU | 0.302 | 209.64 | 1.4351 | 0.08047 |

#### *4.1.4.4 Selection of the Critical Effect*

These studies observed a range of respiratory tract effects. Nasal effects were among the most sensitive, representing a spectrum of effects ranging from those considered mild to more severely adverse in nature, from Bowman's gland and basal cell hyperplasia to olfactory epithelial degeneration. The $POD_{HEC}$ values for these nasal effects (based on $BMCL_{10}$ modeling) are relatively similar and range from 0.02 to 0.071 mg/m$^3$ (results for both sexes combined, Table 20). ReVs are generally based on a mild rather than a more severe adverse effect (see Section 3.6.1.3 of TCEQ 2015a). Bronchiolo-alveolar hyperplasia was among the most sensitive of effects. The $POD_{HEC}$ for this effect (0.05536 mg/m$^3$) is within the range of $POD_{HEC}$ values (0.0138-0.06 mg/m$^3$) for the continuum of MDI-induced nasal effects observed in these studies. The $POD_{HEC}$ of 0.05536mg/m$^3$ for bronchiolo-alveolar hyperplasia is similar to those for Bowman's gland and basal cell hyperplasia in the nose (0.02-0.031 mg/m$^3$) while still less than those for olfactory epithelial degeneration (0.071 mg/m$^3$) and pulmonary interstitial fibrosis (0.080 mg/m$^3$), which are more severe adverse effects. Therefore, while hyperplasia is an effect that may or may not be characterized as mildly adverse (see Table B-1 of TCEQ 2015), as its $POD_{HEC}$ is just below those for more serious adverse effects on the continuum of PMDI-induced respiratory tract effects, the TCEQ is not being unduly conservative. Following duration adjustment and the application of appropriate uncertainty factors, we expect a chronic ReV based on the $POD_{HEC}$ for bronchiolo-alveolar hyperplasia to not only preclude more serious effects but to also be health-protective for the entire spectrum of respiratory tract effects observed in these studies (i.e., both lung and nasal effects).

### 4.1.5 Adjustments of the $POD_{HEC}$

The $POD_{HEC}$ of 0.05536 mg/m$^3$ for bronchiolo-alveolar hyperplasia in female rats was used to derive the chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for MDI and HDI aerosol. The following UFs were applied to the $POD_{HEC}$ (Total UF = 30):

- a $UF_H$ of 10 for intraspecies variability. A lower $UF_H$ is not supported as no data were identified suggesting that potentially sensitive subpopulations would be similarly sensitive to PMDI exposure as the general population;
- a $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not potential toxicodynamic differences; and
- $UF_D$ of 1 was used in consideration of the overall database. There are two 2-yr chronic studies, one subchronic study, as well as reproductive/developmental studies conducted in rats for MDI aerosol. The chronic Rev POD is also supported by an evaluation of nine occupational exposure studies by DFG (1997). Although these studies had limitations, DFG identified an approximate NOAEL of 0.05 mg/m$^3$ for respiratory symptoms in occupational workers, which shows excellent agreement with the BMDL/$POD_{HEC}$ of 0.05536 mg/m$^3$ for

bronchiolo-alveolar hyperplasia in female rats (Table 20). Similar to HDI vapor being used as a toxicity surrogate for MDI vapor (see Section 4.2), a subchronic toxicity study of HDI aerosol supports the conservativeness of the chronic PMDI aerosol POD. More specifically, the subchronic rat NOAEL/$POD_{HEC}$ for HDI aerosol-induced respiratory tract effects (0.6212 $mg/m^3$) supports the conservativeness of the chronic BMDL/$POD_{HEC}$ (0.05536 $mg/m^3$) for PMDI aerosol (e.g., 0.6212 $mg/m^3$ / $UF_{Sub}$ of 6 = 0.1035 $mg/m^3$). Lastly, although reproductive/developmental study results are not available in another species and no two-generation reproductive study is included among the available reproductive/developmental studies, rat study results for both PMDI and HDI vapor support the conservativeness of the POD for the chronic ReV. For example, the LOAELs (≈9-12 $mg/m^3$) identified in PMDI reproductive/developmental toxicity studies are higher than all $BMC_{10}$ values in Table 17. This is not particularly surprising given the high reactivity of diisocyanates (e.g., with water), or that respiratory tract tissue doses of $^{14}C$-labeled MDI (µg equivalent of MDI per gram of tissue) were orders of magnitude higher than those in the gonads of male Wistar rats at 0, 8, 24, and 168 h following exposure to 2 $mg/m^3$ aerosol for 6 h (Table III of Gledhill et al. 2005). Additionally, as another reactive diisocyanate, neither short- nor long-term reproductive/developmental rat studies for HDI vapor showed developmental or reproductive effects. For example, no reproductive/developmental/neurological effects were observed in Astroff et al. (2000b) at multiple-day, repeated exposure concentrations up to 2.033 $mg/m^3$, a reproductive/developmental NOAEL higher than even the $BMC_{10}$ for the PMDI critical effect (0.660 $mg/m^3$). Like PMDI aerosol, respiratory tract effects appeared to be more sensitive for HDI vapor. The reactivity of diisocyanates in conjunction with study results demonstrating respiratory tract effects at lower concentrations than, or in the absence of, developmental/reproductive effects mitigates concern about reproductive/developmental effects being more sensitive than respiratory tract effects. These considerations (i.e., chronic/subchronic PMDI study results for rats and humans, subchronic study results for another diisocyanate (PHDI), reproduction/developmental study results for PMDI and HDI vapor and their reactivity at the point of exposure) inform and support the chronic POD for PMDI as conservative such that the chronic ReV is expected to be protective against potential reproductive/developmental effects. Thus, the protectiveness of the POD for deriving the chronic ReV is strongly supported by considerable data. Accordingly, confidence in the overall database is considered medium-to-high. The quality of the key rat study is high.

Chronic ReV = $POD_{HEC}$ / ($UF_H$ x $UF_A$ x $UF_D$)
= 0.05536 $mg/m^3$ / (10 x 3 x 1)
= 0.001845 $mg/m^3$
= 1.8 µg/$m^3$ (rounded to two significant figures)

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

The $^{chronic}ESL_{threshold(nc)}$ of 0.55 µg/m$^3$ for MDI and HDI is based on the chronic ReV of 1.8 µg/m$^3$ multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 21).

**Table 21. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for MDI and HDI Aerosol**

| Parameter | Summary |
|---|---|
| Study | Reuzel et al. 1994b (re-examined by Feron et al. 2001) |
| Study Population | Female Wistar rats (60/group) |
| Study Quality | High |
| Exposure Method | Inhalation exposure (whole body) to 0, 0.2, 1.0, or 6.0 mg/m$^3$ |
| Exposure Duration | 6 h/d, 5 d/wk for 2 yrs |
| Critical Effects | Bronchiolo-alveolar hyperplasia in female rats |
| POD | 0.216 mg/m$^3$ ($BMCL_{10}$) |
| $POD_{ADJ}$ | 0.039 mg/m$^3$ ($BMCL_{ADJ}$) |
| $POD_{HEC}$ | 0.05536 mg/m$^3$ ($BMCL_{HEC}$) |
| Total UFs | 30 |
| *Interspecies UF* | 3 |
| *Intraspecies UF* | 10 |
| *Incomplete Database UF*<br>*Database Confidence* | 1<br>Medium-High |
| **Chronic ReV (HQ = 1)** | **1.8 µg/m$^3$** |
| **$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)** | **0.55 µg/m$^3$** |

## 4.1.7 Comparison of Results

Table 22 is a summary of the chronic toxicity values derived by the TCEQ and other agencies.

**Table 22. Comparison of the Chronic Toxicity Values for MDI (Aerosol/Vapor) among Agencies**

| | TCEQ | USEPA (1998) | ATSDR (2018) | OEHHA (2016) |
|---|---|---|---|---|
| **Toxicity Value** | 1.8 µg/m$^3$ [a] | 0.6 µg/m$^3$ [b] | 1 µg/m$^3$ [b] | 0.08 µg/m$^3$ [b] |
| Study | Feron et al. 2001 | Reuzel et al. 1994b | Reuzel et al. 1994b | Hoymann et al. (Ernst et al. 1998) |
| Critical Effects | Bronchiolo-alveolar hyperplasia in female rats | Basal cell hyperplasia of the olfactory epithelium in the nasal cavity | Basal cell hyperplasia of the olfactory epithelium in the nasal cavity | Pulmonary interstitial fibrosis |
| POD | 0.216 mg/m$^3$ ($BMCL_{10}$) | --- | 0.48 mg/m$^3$ ($BMCL_{10}$) | 0.0256 mg/m$^3$ ($BMCL_{05}$) |
| $POD_{ADJ}$ | 0.039 mg/m$^3$ ($BMCL_{ADJ}$) | 0.14 mg/m$^3$ ($BMCL_{ADJ}$) | 0.086 mg/m$^3$ ($BMCL_{ADJ}$) | 0.0137 mg/m$^3$ ($BMCL_{ADJ}$) |
| RDDR | 1.4351 | 0.453 | 0.453 | 3.41 |
| $POD_{HEC}$ ($POD_{ADJ}$ x RDDR) | 0.05536 mg/m$^3$ ($BMCL_{HEC}$) | 0.06 mg/m$^3$ ($BMCL_{HEC}$) | 0.039mg/m$^3$ ($BMCL_{HEC}$) | 0.0137 mg/m$^3$ ($BMCL_{HEC}$) |
| Total UFs | 30 | 100 | 30 | 600 |
| Interspecies UF | 3 | 3 | 3 | 6 (2 for toxicokinetic and 3 for toxicodynamic) |
| Intraspecies UF | 10 | 10 | 10 | 100 (10 for toxicokinetic and 10 for toxicodynamic) |
| Incomplete Database UF | 1 | 3 (for the lack of reproductive data) | NA | NA |

[a] Used for MDI aerosol only
[b] Used for both MDI aerosol and vapor

The USEPA calculated a reference concentration (RfC) of 0.6 µg/m$^3$ based on a $POD_{HEC}$ of 0.06 mg/m$^3$ from Reuzel et al. (1994b) by applying a total UF of 100 (3 for interspecies UF, 10 for human variability, and 3 for the lack of reproductive data). The ATSDR chronic MRL of 1 µg/m$^3$ was calculated based on a $POD_{HEC}$ of 0.039 mg/m$^3$ from Reuzel et al. (1994b) by applying a total UF of 30 (3 for interspecies UF and 10 for human variability). The TCEQ ReV of 1.8 µg/m$^3$ was

calculated based on a $POD_{HEC}$ of 0.05536 mg/m$^3$ ($BMCL_{HEC}$) from the Reuzel et al. (1994b) study of female rats (re-examined by Feron et al. 2001) by applying a total UF of 30 (3 for interspecies UF, 10 for human variability, and 1 for incomplete database).

The Reuzel et al. (1994b) study was selected by CalEPA as the key study to derive an 8-h reference exposure level (REL) of 0.16 µg/m$^3$ based on a $BMCL_{05}$ value of 0.118 mg/m$^3$. The CalEPA OEHHA calculated a chronic REL of 0.08 µg/m$^3$ based on a $BMCL_{05}$ of 0.026 mg/m$^3$ for pulmonary interstitial fibrosis in rats reported by Hoymann et al. (1998, refers to Ernst et al. 1998 as cited by OEHHA 2016). The CalEPA chronic REL is an order of magnitude lower than either the TCEQ chronic ReV or the ATSDR chronic MRL. It should be noted that the CalEPA used an unusually high RDDR (3.41) to calculate its $POD_{HEC}$ and applied much higher total UFs (600) to its $POD_{HEC}$ while the TCEQ, USEPA, and ATSDR all used much lower total UF values and RDDRs of 1.1588, 0.453, and 0.453, respectively, based on MPPD modeling. It should be noted that the toxicity values derived by the USEPA, CalEPA, and ATSDR are applied to both MDI aerosol and vapor.

## *4.2 Noncarcinogenic Potential of MDI and HDI Vapor*

The target organ of MDI and HDI vapor toxicity in humans is the respiratory tract, with most exposures resulting from inhaling vapors from MDI/HDI monomer or its prepolymers. Respiratory effects of MDI and HDI have been reported in several human case reports or epidemiologic studies, however, these studies have difficulties (e.g., inaccurate exposure data, confounding factors) in relating a specific effect in humans to exposure to MDI or HDI vapor in the workplace.

No chronic inhalation studies with MDI vapor are reported in any mammalian species and thus, chronic toxicity factors for MDI vapor are not derived. For air permits review of MDI vapors, the chronic ESL derived for HDI vapor will be used.

### 4.2.1 Key and Supporting Studies

#### *4.2.1.1 Key Study – Shiotsuka et al. (1989)*

A combined chronic toxicity/oncogenicity study was conducted by Mobay Chemical Corp. (Shiotsuka et al. 1989, as cited in USEPA 1994, ATSDR 1998, and OECD 2001). In this study, which was conducted according to GLP-OECD Guideline 453, Fischer 344 rats were exposed (whole body) to 0, 0.005, 0.025, or 0.164 ppm (mean analytical concentrations) HDI vapor for 6 h/d, 5 d/wk for one or two yrs. There were no significant differences in mortality and organ weights between treated and control groups. Transient ocular irritation in males, small (5%) but statistically significant decreases in body weight of females, and slight anemia in females were observed at 0.164 ppm. HDI-related histopathological changes were limited to the nasal cavity and lungs. Lung lesions (no clear dose-response) were only observed in the 0.025 and 0.164 ppm groups (both sexes). A NOAEL and LOAEL of 0.005 and 0.025 ppm, respectively, for lung lesions were identified.

Nasal lesions observed after 1 yr of exposure in rats were restricted to the nasal mucosa at all exposure concentrations. All these lesions were also observed after two yrs of exposure. The most prominent lesion was dose-responsive severe degenerative changes in the olfactory epithelium observed in rats exposed to 0.164 ppm. These lesions were absent at the lowest concentration (0.005 ppm), with parallel increases in both incidence and severity at the two highest concentrations (0.025 and 0.164 ppm). The level of 0.025 ppm was judged by the study authors to be a LOAEL. Other nasal lesions (hyperplasia/metaplasia, mucus hyperplasia, and inflammation) occurred at increased incidence compared with controls in both the low- and mid-exposure groups, but the severity was either lower or unchanged compared to controls. The character of the lesions in the nasal tract was considered adaptive rather than adverse by USEPA (1994) and Foureman et al. (1994). On the other hand, degeneration of olfactory epithelium showed clearly adverse toxic responses for both incidence and severity and was

considered as adverse effect by the USEPA IRIS (1994). The level of 0.005 ppm was used as a NOAEL (for degeneration of olfactory epithelium) by the USEPA IRIS (1994) to derive its RfC. This level, however, was considered by the ATSDR (1998) as a minimal LOAEL for nasal epithelial hyperplasia and was used to derive its chronic MRL. Consistent with USEPA, the TCEQ used the level of 0.005 ppm (5 ppb) as a NOAEL for degeneration of olfactory epithelium to derive the chronic ReV and ESL for HDI vapor.

### *4.2.1.2 Supporting Studies*

#### 4.2.1.2.1 Shiotsuka et al. (1988, as cited in OECD 2001)

A 90-d inhalation study was conducted with HDI by Mobay Corp. (Shiotsuka et al. 1988, as cited in ATSDR 1998 and OECD 2001), and it followed the OECD Guideline 413. Male and female Fischer 344 rats (20/sex/group) were exposed (whole body) to vapor concentrations (analytical) of 0, 0.011, 0.041, or 0.143 ppm (0, 0.068, 0.272 or 0.952 mg/m$^3$), 6 h/d for 66-69 d over a period of 13 wks. There were no compound-related effects on mortality, body weight, clinical chemistry, hematology, urinalysis, gross pathology, or organ weights. The only compound-related findings were ocular irritation and histopathologic lesions of the anterior nasal cavity. Transient ocular irritation occurred in all HDI-treated animals. However, transient ocular irritation was only observed in male rats exposed at 0.164 ppm in the Shiotsuka et al. (1989) chronic key study. Hyperplasia and/or squamous metaplasia of the respiratory epithelium were the most important lesions in both sexes. Hyperkeratosis, mucus cell hyperplasia, and inflammatory cell infiltration were also observed in the nasal cavity. These histopathological lesions were observed at all three concentrations. Hyperplasia and/or squamous metaplasia of the respiratory epithelium was often present in the mid- and high-dose rats. The lesions were very mild and were seen in only a few animals (11/40) in the 0.011 ppm exposure group. The concentration of 0.011 ppm (11 ppb) was deemed a NOAEL by the investigators for respiratory tract lesions (USEPA 1994).

#### 4.2.1.2.2 Marek et al. (1999) Study

In a subchronic study for airway hyper-responsiveness conducted by Marek et al. (1999), groups of female guinea pigs (11/group) were exposed to 0 or 10 ppb HDI vapor 6 h/d, 5 d/wk for 1, 2, 4, or 8 wks. HDI vapors were generated in a gas-tight, heated (80-120°C), stainless steel container. Significant time-dependent increases in airway hyper-responsiveness in *ex vivo* lung tissue exposed to acetylcholine (ACH) were observed in guinea pigs exposed to 10 ppb HDI ($p<0.05$). The observed increases in ACH responsiveness were reversible. The level of 10 ppb was a free-standing LOAEL. The LOAEL identified from the Marek et a. (1999) subchronic study was higher than the NOAEL or minimal LOAEL (5 ppb) identified from the Shiotsuka et al. (1989) key chronic study.

### *4.2.1.3 Epidemiologic Studies*

Exposure to low doses of HDI over long periods of time has not been demonstrated to cause changes in respiratory function in human epidemiology studies. In a study by Shepperly and Hathaway (1991, as cited in ATSDR 1998), male workers were identified as having a potential for HDI exposure (n=30) or not (controls, n=30) and then matched according to age, height, smoking history, sex, and race. No estimation of an average exposure for workers potentially exposed to HDI was reported. However, the authors speculated that the actual average exposures, when considering the protection from respirators, were below 5 ppb. Pulmonary function test (PFT) including forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), and mean forced expiratory flow during the middle half of FVC ($FEF_{25-75\%}$) were performed. No statistically significant differences in pulmonary function were observed between the workers with potential HDI exposure and controls. In a follow-up study of this same population by DeWilde and Hathaway (1994, as cited in ATSDR 1998), additional PFTs obtained in 1991, 1992, and 1993 were included. The exposure concentration from working areas was estimated to be between 0.5 and 7 ppb (3.4 and 47.6 µg/$m^3$). Personal monitoring of HDI levels ranged from 0.7 to 3.9 ppb in HDI-exposed workers in 1992 and 0.6 to 1.8 ppb in 1993. No statistically significant differences in PFT were observed in the follow-up study.

The Dewilde and Hathaway (1994) study has been continued through 1997 by Hathaway et al. (1999). In this study, no effect on lung function was found in 43 workers after 6 yrs of occupational exposure to HDI monomer, HDI biuret, and HDI trimer, when they were compared with 42 controls. The average daily high peak exposure was 2.9 ppb. The highest 15-minute, short-term exposure was 4.4 ppb, with an average daily high concentration of 1.5 ppb. Average daily exposures were much lower while in the unit, at approximately 0.5 ppb. The 8-h and 12-h time-weighted averages (TWA) were approximately 0.13 and 0.083 ppb, respectively. Exposures to these levels appear to pose no risk of accelerated decline in pulmonary function. The results suggest that occasional peak exposures to HDI in the 1 to 10 ppb range do not cause accelerated decline in FVC or $FEV_1$.

In a retrospective study, Cassidy et al. (2010) expanded the Hathaway et al. (1999) study by adding workers from an additional plant (Bayer Material Science) over a longer duration of follow-up, yielding a larger cohort of workers (n=100) who were potentially exposed to HDI monomer. A total of 237 personal airborne HDI samples from Bayer Material Science plant were included in the evaluation of employee exposure from 1983 through 2006. The mean air monitoring HDI concentration was 0.78 ppb (ranging from not detectable to 31 ppb). The majority of the collected samples (230) resulted in measured airborne concentrations below 3 ppb; 3 and 4 samples were 3 - 9.99 and > 10 ppb, respectively. A random coefficient regression analysis compared the decline in pulmonary function test values over time. No significantly accelerated annual decline in $FEV_1$ in the HDI exposure group compared to the matched control

group was observed. Retrospective medical review was used to identify potential cases of occupationally induced asthma. No cases of adult onset asthma, beyond those present at time of hire, and no cases of occupational asthma were identified.

Another epidemiological study (Alexandersson et al. 1987) involved 46 male car painters (20–64 yrs of age, average age 34.8 yrs; 63% smokers) who had been exposed to an HDI compound containing 0.5-1% HDI monomer and 40-50% HDI-BT, along with other diisocyantes, for 7 yrs. Car painters were matched against a control group (142 car painters and car mechanics who were not exposed to any diisocyanates) by sex, age, height, and smoking status. The mean exposure to HDI-BT through car painting was 115 $\mu g/m^3$ (6 ppb) (range: 10-385 $\mu g/m^3$ [0.5-19.7 ppb]). The exposure concentration of HDI monomer was 1 $\mu g/m^3$ (0.05 ppb). High short-term exposure peaks of up to 13,500 $\mu g/m^3$ of HDI compound were also noted in this study. Results of a questionnaire indicated that eye, nose, and throat irritation occurred more frequently in car painters than in controls, but the difference was not significant. The only statistically significant different lung function parameter measured was an increase in residual volume in relation to vital capacity (%VC). This difference was attributed to an effect on the small airways and could be consistent with small airway disease associated with diisocyanate exposures. A 6-yr follow-up investigation by Tornling et al. (1990) involved 36 male car painters (average age 39.8 yrs; 55.6% smokers; average duration of employment 16.5 yrs) and 115 controls (average age 38.4 yrs; 56.5% smokers) original investigation by Alexandersson et al. (1987) were reinvestigated. The 36 car painters had been exposed to calculated TWA concentrations of 0.0015 $mg/m^3$ (0.2 ppb) HDI monomer and 0.09 $mg/m^3$ (5 ppb) HDI-BT with peak concentration $\geq 2$ $mg/m^3$ HDI-BT for at least 30 seconds.

No statistically significant decrements in lung function were observed in non-smoking car painters exposed to HDI and HDI-BT when they were compared with non-smoking controls.

In summary, the epidemiologic studies show little effect of HDI vapor human occupational exposure on lung function. However, these studies have weaknesses (e.g., inaccurate exposure data, co-pollutants or other confounding factors) that make it difficult to relate a specific effect in humans to exposure to HDI in the workplace. Therefore, the results of epidemiologic studies were inadequate to derive a chronic ReV and ESL for HDI/HDI polymer.

### *4.2.1.4 Reproductive/Developmental Toxicity Studies*

No information was located regarding reproductive/developmental effects in humans following inhalation exposure to HDI vapor. No reproductive organ lesions at gross necropsy or during histopathological examinations were found in male and female Fischer 344 rats exposed to HDI vapor in concentrations ranging from 0.011 to 0.143 ppm for 6 h/d, 5 d/week, for 66-69 days (Shiotsuka et al. 1988) or in male and female Fischer 344 rats exposed to HDI concentrations ranging from 0.005 to 0.175 ppm for 6 h/d, 5 d/week over a 2-yr period (Shiotsuka et al. 1989).

As described in Section 3.2.1.3, no developmental toxicity was observed up to 0.308 ppm (308 ppb), which is the developmental NOAEL from Astroff et al. (2000b) study.
The NOAELs for developmental effects are higher than the NOAEL (0.005 ppm) for olfactory epithelial degeneration identified from the key chronic study (Shiotsuka et al. 1989). Thus, the derived chronic ReV and ESL are expected to be protective against developmental effects.

## 4.2.2 Mode-of-Action (MOA) Analysis and Dose Metric

As described in Section 3.2.2, the MOA for a lung irritation-based POD is likely to be based on the high reactivity of the diisocyanate group. The MOA for nasal olfactory epithelial degeneration is likely related to the high reactivity of the isocyanate group (DFG 2013, ATSDR 1998). Exposure concentration to the HDI vapor will be used as the dose metric. MOA information indicates that the adverse health effects observed in rats are relevant for humans.

## 4.2.3 Selection of the Key Study, POD and Critical Effect

The chronic NOAEL of 0.005 ppm (5 ppb) for nasal olfactory epithelial degeneration identified from the Mobay Corp study (Shiotsuka et al. 1989) was used as the POD for HDI vapor. The critical effect was olfactory epithelial degeneration.

## 4.2.4 Dosimetric Adjustments

### *4.2.4.1 Exposure Duration Adjustments*

The chronic NOAEL of 0.005 ppm (5 ppb) for nasal olfactory epithelial degeneration identified from the Mobay Corp (Shiotsuka et al. 1989) study was used as the POD for HDI vapor. An adjustment from a discontinuous (6 h/d for 5d/week) to a continuous exposure duration was conducted (TCEQ 2015a) as follows:

$$POD_{ADJ} = 5 \text{ ppb} \times (6/24) \times (5/7) = 0.8929 \text{ ppb}$$

### *4.2.4.2 Default Dosimetric Adjustments from Animal-to-Human Exposure*

Chronic exposures to HDI vapor cause POE effects and HDI was therefore considered as a Category 1 vapor. For Category 1 vapors, a default dosimetric adjustment factor (DAF) of 1 is used, as recommended by the USEPA (2012). Accordingly, the $POD_{HEC}$ = $POD_{ADJ}$ x default DAF. The resulting $POD_{HEC}$ from the $POD_{ADJ}$ of 0.8929 ppb is 0.8929 ppb.

## 4.2.5 Adjustments of the $POD_{HEC}$

The $POD_{HEC}$ of 0.8929 ppb for nasal epithelial hyperplasia was used to derive the chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for MDI and HDI vapor. The following UFs were applied to the $POD_{HEC}$ (Total UF = 30):

- a $UF_H$ of 10 for intraspecies variability. A lower $UF_H$ is not supported as no data were identified suggesting that potentially sensitive subpopulations would be similarly sensitive to HDI vapor exposure as the general population;
- a $UF_A$ of 3 for interspecies variability because a default dosimetric adjustment was conducted to account for toxicokinetic differences between animals and humans but not toxicodynamic differences.
- $UF_D$ of 1 was used in consideration of the overall database. There is one chronic study (rats) and two subchronic studies (rats or guinea pigs) conducted for different toxicity endpoints in inhalation bioassays. The chronic NOAEL/$POD_{HEC}$ identified from these studies (0.8929 ppb) appears generally consistent with levels not associated with effects in the limited epidemiological studies available (Section 4.2.1.3). While there is no two-generation reproductive study available, neither short- nor long-term reproductive/developmental studies for HDI vapors in rats showed developmental or reproductive effects (Sections 3.2.1.3 and 4.2.1.4). For example, while no reproductive/developmental/neurological effects were observed in Astroff et al. (2000b) at multiple-day, repeated exposure concentrations up to 299 ppb, respiratory tract effects were observed at ≥ 53 ppb and included those more serious in nature (e.g., degeneration of the olfactory epithelium), similar to the ≥ 25 ppb causing these effects in the key study (Shiotsuka et al. 1989). Respiratory tract effects also appeared to be more sensitive for another reactive diisocyanate aerosol, PMDI. The reactivity of diisocyanates, in conjunction with HDI vapor study results demonstrating numerous respiratory tract effects (including those more severely adverse) in the absence of developmental/reproductive effects at even higher exposure concentrations, mitigates concern about reproductive/developmental effects being more sensitive than respiratory tract effects. These considerations (i.e., chronic/subchronic HDI data, reproduction/developmental study result LOAELs and NOAELs for HDI vapor (and PMDI aerosol) and reactivity at the point of exposure) inform and support the chronic POD as conservative such that the chronic ReV is expected to be protective against potential reproductive/developmental effects. Thus, the protectiveness of the POD for deriving the chronic ReV is strongly supported by considerable data for HDI vapor (as well as data for HDI and MDI aerosols). Accordingly, confidence in the overall database is considered medium-to-high. The quality of the key rat study is high.

Chronic ReV = $POD_{HEC}$ / ($UF_H$ x $UF_A$ x $UF_D$)

= 0.8929 ppb / (10 x 3 x 1)
= 0.8929 ppb / 30
= 0.02976 ppb
= 0.030 ppb or 0.21 µg/$m^3$ (rounded to 2 significant figures)

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

The $^{chronic}$ESL of 0.063 µg/$m^3$ for HDI vapor is based on the chronic ReV of 0.21 µg/$m^3$ multiplied by a HQ of 0.3 and rounded to two significant figures at the end of all calculations (Table 23).

**Table 23. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$ for MDI and HDI Vapor**

| Parameter | Summary |
|---|---|
| Study | Shiotsuka et al. 1989 (Mobay Inc. 1989) |
| Study Population | Fischer 344 rats (60/sex/group) |
| Study Quality | High |
| Exposure Method | Inhalation exposure (whole body) to 0, 0.005, 0.025, or 0.164 ppm HDI vapor |
| Exposure Duration | 6 h/d, 5 d/week for 2 yrs |
| Critical Effects | Degeneration of olfactory epithelium in the nasal cavity |
| POD | 0.005 ppm (5 ppb) (NOAEL) |
| $POD_{ADJ}$ | 0.8929 ppb |
| $POD_{HEC}$ | 0.8929 ppb |
| Total UFs | 30 |
| *Interspecies UF* | 3 |
| *Intraspecies UF* | 10 |
| *Subchronic UF* | NA |
| *Incomplete Database UF* | 1 |
| *Database Quality* | Medium-High |
| **Chronic ReV (HQ = 1)** | **0.21 µg/$m^3$** |
| **$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)** | **0.063 µg/$m^3$** |

## 4.2.10 Comparison of Results

Table 24 is a summary of the chronic toxicity values derived by the TCEQ and other agencies.

**Table 24. Comparison of the Chronic Toxicity Values for HDI Vapor among Agencies**

| | TCEQ | ATSDR (1998) | USEPA (1994) |
|---|---|---|---|
| Toxicity Value | 0.2 µg/m$^3$ (0.03 ppb) | 0.07 µg/m$^3$ (0.01 ppb) | 0.01 µg/m$^3$ |
| Study | Shiotsuka 1989 (Mobay Inc. 1989) | Mobay Inc. 1989 | Mobay Inc. 1989 |
| Critical Effects | Degeneration of olfactory epithelium in nasal cavity | Adaptive nasal epithelial response | Degeneration of olfactory epithelium in nasal cavity |
| POD | 0.005 ppm (5 ppb) (NOAEL) | 0.005 ppm (minimal LOAEL) | 0.005 ppm (0.035 mg/m$^3$) (NOAEL) |
| $POD_{ADJ}$ | 0.8929 ppb (6 µg/m$^3$) | 0.005 ppm | 0.006 mg/m$^3$ (6 µg/m$^3$) |
| RGDR | 1 (default DAF) | 0.183 | 0.183 |
| $POD_{HEC}$ ($POD_{ADJ}$ x RGDR) | 0.8929 ppb (6 µg/m$^3$) | 0.9 ppb (6.19 µg/m$^3$) | 1 µg/m$^3$ (0.145 ppb) |
| Total UFs | 30 | 90 | 100 |
| Interspecies UF | 3 | 3 | 3 |
| Intraspecies UF | 10 | 10 | 10 |
| LOAEL to NOAEL UF | -- | 3 | -- |
| Incomplete Database UF | 1 | -- | 3 (for the lack of developmental/ reproductive studies) |

The ATSDR (1998) chronic MRL of 0.01 ppb (0.07 µg/m$^3$) was calculated based on a POD (minimal LOAEL) of 0.005 ppm for an adaptive nasal cavity epithelial response in rats from the Mobay Inc. 1989 study. No duration adjustment was made for the MRL POD. A $POD_{HEC}$ of 0.9 ppb was calculated by multiplying by an RGDR of 0.183. The RfC was derived by applying total UFs of 90 to the $POD_{HEC}$.

The USEPA IRIS (1994) calculated a reference concentration (RfC) of 0.01 µg/m$^3$ based on a POD (NOAEL) of 0.005 ppm (0.035 mg/m$^3$) for degeneration of olfactory epithelium in rats reported

by Mobay Inc 1989. The POD was then adjusted to a $POD_{ADJ}$ of 0.8929 ppb (6 µg/$m^3$) for continuous exposure. A $POD_{HEC}$ of 0.001 mg/$m^3$ was calculated from the $POD_{ADJ}$, multiplied by an RGDR of 0.183. The RfC was derived by applying total UFs of 100 to the $POD_{HEC}$.

The TCEQ ReV was calculated based on the same $POD_{ADJ}$ of 0.8929 ppb by applying a default RGDR of 1 according to the updated USEPA (2012) inhalation dosimetry guidance, and total UFs of 30 (3 for interspecies UF, 10 for human variability, and 1 for incomplete database).

The chronic USEPA RfC is more than an order of magnitude lower than the TCEQ chronic ReV. The USEPA (1994) used a much lower and out of date RGDR (0.183) to calculate its $POD_{HEC}$ while the TCEQ used a default DAF of 1 according to the updates of inhalation gas dosimetry by the USEPA (2012), because chronic exposure to HDI vapor cause POE effects (Category 1 vapor). Additionally, the USEPA used a UF of 3 to account for the lack of developmental/reproductive studies while the TCEQ used a database UF of 1 for reasons described in Section 4.2.5.

## *4.3 Carcinogenic Potential*

### 4.3.1 MDI

Numerous *in vitro* mutagenicity studies have been conducted on MDI that do not show mutagenic potential, except under conditions using solvents which cause rapid hydrolysis of MDI to MDA. USEPA (1998) indicated that the mutagenic potential is only of marginal value with respect to assessment of cancer potential. MDI has been shown to be mutagenic in some Salmonella strains, but not others. Moreover, target tissue data are highest on the scientific evidence hierarchy for evaluating mutagenic potential, especially following *in vivo* exposure of the most relevant study species/strain for tumors via the most relevant exposure route and dosing regimen, whereas *in vitro* testing results are low hierarchal data. The USEPA indicated that the available evidence is inadequate to describe the carcinogenic potential of PMDI/MDI (USEPA 1998).

#### *4.3.1.1 Reuzel et al. (1994b)*

Carcinogenicity was assessed in the Reuzel et al. (1994b) 2-yr animal (Wistar rat) study with PMDI. No adverse effects on the distribution and incidence of tumors were found, with the exception of tumors in the lungs. Primarily benign lung tumors (adenomas) in Type II cells were seen at the highest concentration (6 mg/$m^3$) (6/60 males and 2/59 females). The adenomas were located adjacent to areas in which hemorrhage, macrophage accumulation, and fibroblastic reactions were observed. One pulmonary adenocarcinoma was observed in one male (1/60) exposed to this concentration of PMDI. The investigators considered the adenomas and adenocarcinoma observed in this study to be treatment related. Based on results observed in the Reuzel et al. (1994b) 2-yr animal study, the USEPA (1998) suggests that PMDI has tumorigenic potential. However, the USEPA also indicates that the finding of one pulmonary adenocarcinoma in a chronic study is not clear evidence of carcinogenic potential. Reuzel et al. (1994b) also concluded that pulmonary adenomas are considered morphologically to be a stage in the progression from recurrent alveolar wall damage by PMDI and/or PMDI-containing AM leading to hyperplasia (alveolar bronchiolization in the subpleural regions) and ultimately to bronchioloalveolar tumors and/or to carcinoma. Thus, in addition to the lack of clear evidence of carcinogenic potential cited by USEPA (and lack of malignant tumor data to sufficiently characterize the shape of any dose-response curve for carcinogenicity in this study as tumors were a high-dose phenomenon, with only a single adenocarcinoma), the authors' conclusions concerning the etiology of tumors support the conclusion that the prevention of pulmonary damage (i.e., recurrent alveolar wall damage) will preclude the potential progression of recurrent damage to adenomas and/or carcinoma.

#### *4.3.1.2 Hoymann et al. (1995)*

USEPA (1998) reports no treatment-related increase in pulmonary adenomas in the female rats exposed to pure MDI monomer in the Hoymann et al. (1995) study. The occurrence of lung tumors was limited to a bronchiolo-alveolar adenoma observed in 1/80 female rats exposed to 2.05 mg/m$^3$ MDI. The USEPA indicates that the absence of a treatment-related increase in pulmonary adenomas at a concentration lower than in the Reuzel (1994b) study may be due to the female Wistar rat or strain being less susceptible, or due to the nature of monomeric MDI compared to PMDI.

In conclusion, the USEPA indicates that considering the finding of one pulmonary adenocarcinoma in the Reuzel et al. (1994b) chronic study and the absence of lung adenomas in the Hoymann et al. (1995) study, there is not clear evidence of carcinogenic potential of MDI. Thus, USEPA concluded that PMDI/MDI should be either unclassified or classified as a Group D chemical.

According to the International Research on Cancer (IARC 1999), there is “inadequate evidence” for the carcinogenicity of MDI or PMDI in humans, and there is “limited evidence” that MDI or PMDI is carcinogenic to experimental animals. Therefore, IARC concluded that MDI or PMDI is not classifiable as to its carcinogenicity to humans (Group 3). USEPA (1998) has characterized the carcinogenicity of MDI/polymeric MDI as “cannot be determined, but for which there is suggestive evidence that raises concern for carcinogenic effects”. Because of the general lack of evidence of carcinogenicity of MDI or PMDI (as well as the lack of sufficient dose-response data and carcinogenic classification by corollary), we did not develop a chronic ESL based on carcinogenesis, consistent with TCEQ guidelines (TCEQ 2015a). Furthermore, it is noted that the POD ($BMCL_{10}$ of 0.216 mg/m$^3$) used to develop the chronic ReV based on non-cancer respiratory effects is well below the PMDI concentration that produced tumors (6 mg/m$^3$), which the authors attributed to recurrent lung damage that the chronic ReV should protect against.

### 4.3.2 HDI

No information is available on the carcinogenic effects of HDI in humans. HDI was not mutagenic when tested against Salmonella typhimurium strains TA100, TA98, and TA1537 with or without metabolic activation (Anderson et al. 1980, as cited in ATSDR 1998). HDI showed no clastogenic activity in mice exposed once to HDI vapors up to 1.5 ppm for 6 h (OECD 2001). No compound-related oncogenicity was observed in the combined chronic toxicity/oncogenicity study (Mobay Inc. 1989). The results of oncogenicity portion of the 2-yr Mobay Inc. (1989) were further reported by Shiotsuka et al. (2010). Briefly, groups of male and female Fischer-344 rats (60/sex/group) were exposed whole-body to mean analytical air concentrations (± standard deviation) of 0, 0.005±0.002, 0.025±0.006, and 0.164±0.037 ppm HDI 6 h/d, 5 d/wk for

2 yrs. As described in Section 4.2.1.1, HDI-related histopathological changes were limited to the nasal cavity (degeneration of olfactory epithelium). There was no evidence of progression of these changes in the nasal epithelium to neoplasia nor evidence of any compound-related neoplastic lesions for any of the other tissues examined. No statistically significant differences were found for the incidence of neoplastic changes in HDI-exposed rats compared to controls. The investigators concluded that HDI did not show carcinogenic potential in this study. The USEPA has not classified HDI for carcinogenicity.

## *4.4 Welfare-Based Chronic ESL*

There are insufficient data to establish an effect on vegetation as a result of chronic exposure to HDI vapor or aerosol.

## *4.5 Long-Term ESL and Values for Air Monitoring Data Evaluations*

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

### 4.5.1 MDI and HDI Aerosol

- chronic ReV = 1.8 µg/m$^3$
- $^{chronic}ESL_{threshold(nc)}$ = 0.55 µg/m$^3$

For MDI and HDI aerosol, the long-term ESL for air permit evaluations is 0.45 µg/m$^3$.

### 4.5.2 MDI and HDI Vapor

- chronic ReV = 0.21 µg/m$^3$
- $^{chronic}ESL_{threshold(nc)}$ = 0.063 µg/m$^3$

For MDI and HDI vapor, the long-term ESL for air permit evaluations is 0.063 µg/m$^3$ (0.0090 ppb).

## *4.6 Chronic Inhalation Observed Adverse Effect Levels (IOAELs)*

### 4.6.1 MDI and HDI Aerosol

The $BMC_{10}$ of 0.660 mg/m$^3$ for bronchiolo-alveolar hyperplasia in female rats identified from the Reuzel et al. (1994b) MDI/PMDI 2-yr aerosol study (re-examined by Feron et al. 2001) was used as the POD for estimation of a chronic inhalation observed adverse effect level ($^{chronic}$IOAEL). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. The $BMC_{10}$ of 0.660 mg/m$^3$ was then adjusted to $BMC_{10HEC}$. The calculated $BMC_{10HEC}$ is then used as the $^{chronic}$IOAEL.

For MDI/PMDI aerosol, the $BMC_{10HEC}$ was calculated from the $BMC_{10}$ multiplied by a RDDR of 1.1588 (Table 20).

$$BMC_{10HEC} = BMC_{10} \times RDDR_{ET} = 0.660 \text{ mg/m}^3 \times 1.1588 = 0.76 \text{ mg/m}^3$$

Effects occurred in some animals and the $^{chronic}$IOAEL 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 was used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The $^{chronic}$IOAEL level is provided for informational purposes only (TCEQ 2015a). The $^{chronic}$IOAEL for MDI/PMDI aerosol is:

MDI/PMDI aerosol $^{chronic}$IOAEL = 0.76 mg/m$^3$ (rounded to 2 significant figures)

The margin of exposure between the estimated $^{chronic}$IOAEL (0.76 mg/m$^3$) and the chronic ReV (1.8 µg/m$^3$) for MDI/PMDI aerosol is a factor of 410.

## 4.6.2 HDI Vapor

The LOAEL of 0.025 ppm (25 ppb) for olfactory cell degeneration in the nasal cavity of rats identified from the Shiotsuka et al. (1989) 2-yr HDI vapor study was used as the POD for calculation of a chronic inhalation observed adverse effect level ($^{chronic}$IOAEL). No duration adjustments were made although animal-to-human dosimetric adjustments were performed. The LOAEL of 25 ppb was then adjusted from an animal concentration to a $LOAEL_{HEC}$. The calculated $LOAEL_{HEC}$ is then used as the $^{chronic}$IOAEL.

For HDI vapor (Category 1 vapor), the $LOAEL_{HEC}$ was calculated from the LOAEL multiplied by a default RGDR of 1 (see Section 3.2.6.2.1).

$$LOAEL_{HEC} = LOAEL \times RGDR = 25 \times 1 = 25 \text{ ppb}$$

Effects occurred in some animals and the $^{chronic}$IOAEL 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 (i.e., chronic exposure). Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The $^{chronic}$IOAEL level is provided for informational purposes only (TCEQ 2015a). The $^{chronic}$IOAEL for HDI vapor is:

HDI $^{chronic}$IOAEL = 25 ppb

The margin of exposure between the $^{chronic}$IOAEL (25 ppb or 170 µg/m$^3$) and the chronic ReV (0.030 ppb or 0.21 µg/m$^3$) for HDI vapor is a factor of 833.

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# Appendix 1. MPPD Program Outputs for Key Studies

## *1.1 MPPD Program Output for Acute Key PMDI Aerosol Study - Pauluhn et al. (1999)*

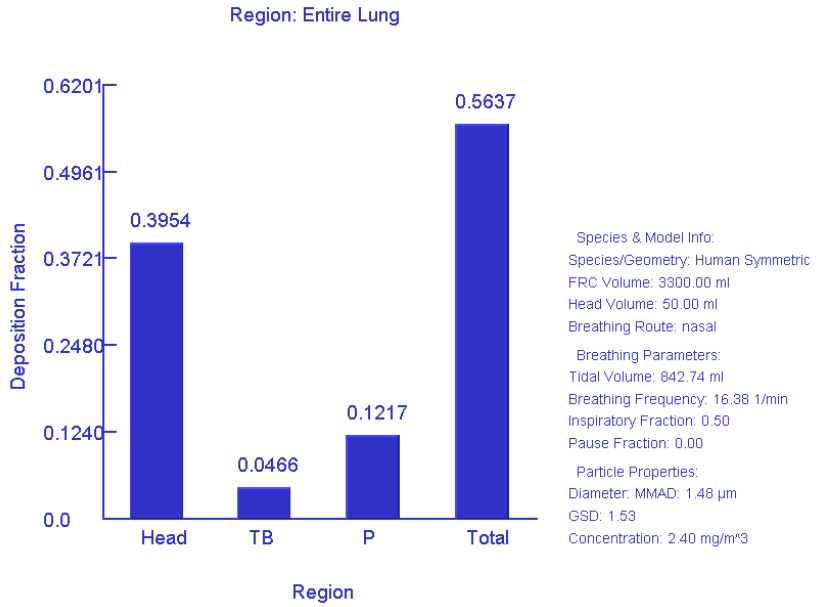


**Figure 1. Human output from the MPPD model used in the acute section**

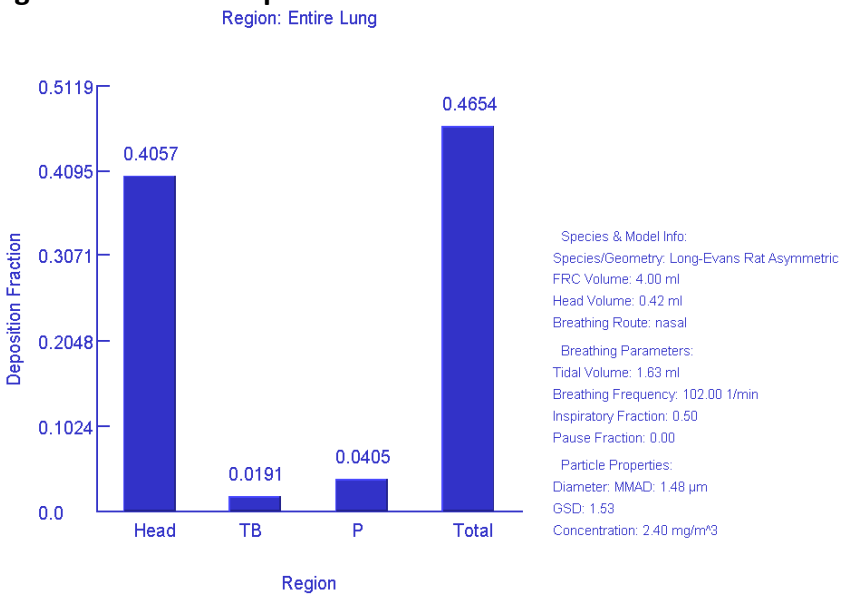


**Figure 2. Rat output from the MPPD model used in the acute section**

## *1.2 MPPD Program Output for Chronic Key PMDI Aerosol Study – Reuzel et al. (1994b)*

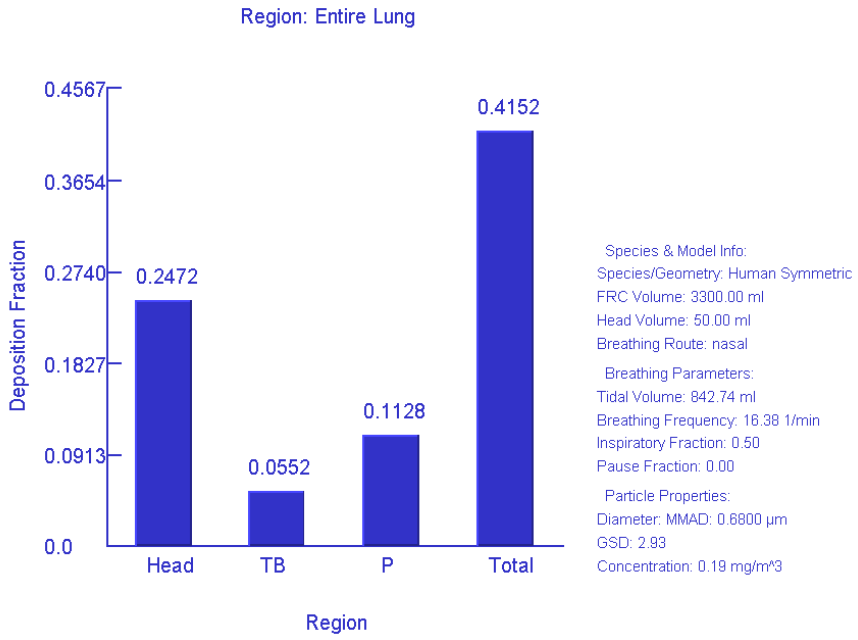


**Figure 3. Human output from the MPPD model used in the chronic section**

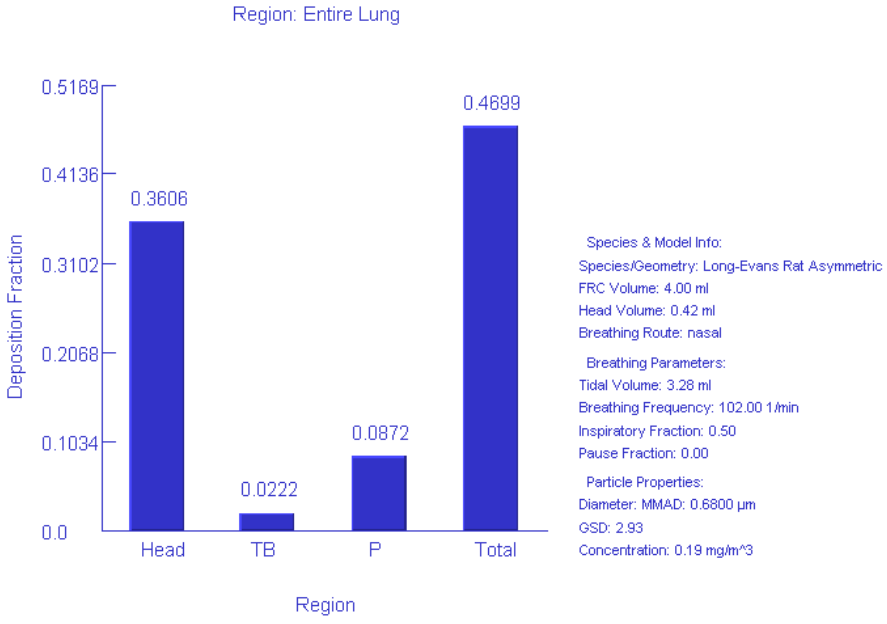


**Figure 4. Rat output from the MPPD model used for male rats in the chronic section**

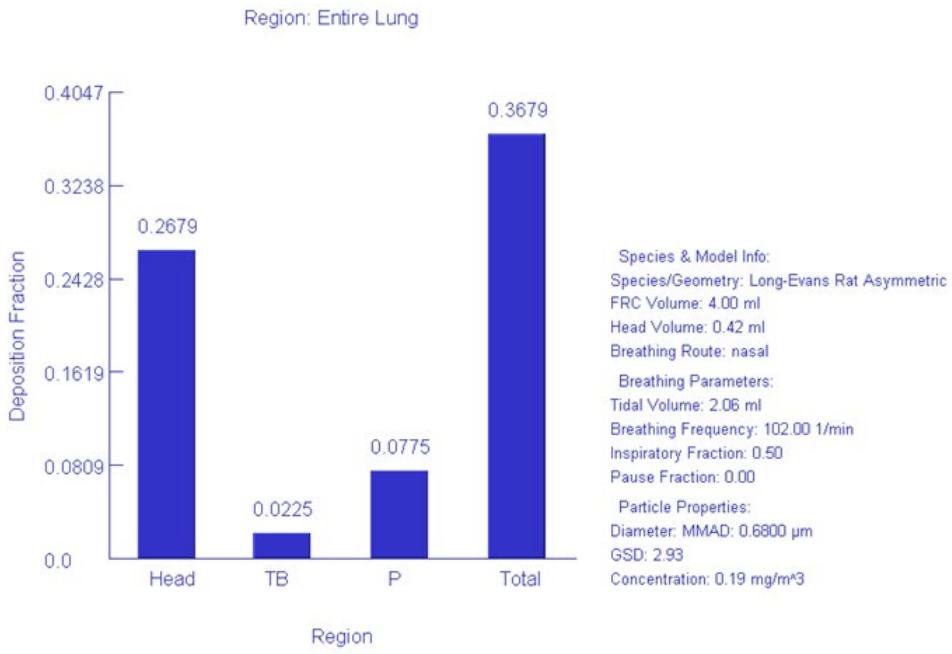


**Figure 5. Rat output from the MPPD model used for female rats in the chronic section**

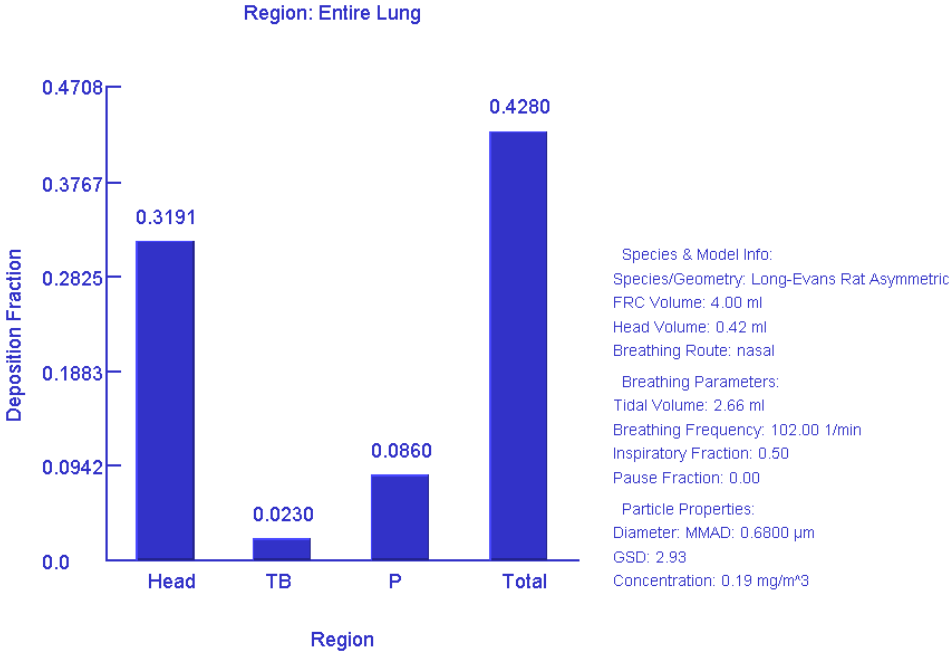


**Figure 6. Rat output from the MPPD model used for combined rats in the chronic section**

# Appendix 2. Default Dosimetric Adjustments from Animal-to-Human Exposure

## *Polymeric HDI Aerosol from the Lee et al. (2003) Acute Study*

Default dosimetric adjustments from animal-to-human exposure were conducted for the mouse study to determine the calculated $POD_{HEC}$ for each endpoint. In the key study, an aerosol of polymeric HDI trimer 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 polymeric HDI trimer aerosol in the target respiratory region.

Parameters necessary for this program are particle diameter, particle density, chemical concentration, and pulmonary regions considered. According to Lee et al. (2003), the MMAD of polymeric HDI trimer aerosol used in their study was 0.81 µm with a GSD of 1.2. The particle density is 1.14 g/cm$^3$ (Table 3). The chemical concentration is the $POD_{ADJ}$ of 2.223 mg/m$^3$. Because the polymeric HDI trimer particle sizes are small enough and the critical effects were identified from BAL fluids, the target region for polymeric HDI trimer aerosol was considered the total particle distribution for the tracheobronchial (TB) and pulmonary (PU) regions. Since body weights were not provided, a default body weight of 0.0316 kg for B6C3F1 mice was used (USEPA 1994). Minute volume (36.8342 mL/min) was calculated using this average body weight, and a default breathing frequency (160 breaths/min) and tidal volume (0.23 mL) were used. All remaining values used were default. Once the total particle distribution for the mouse ($DF_A$ = 0.0898) and human ($DF_H$ = 0.129) were determined, the Regional Deposition Dose Ratio (RDDR) was calculated as follows:

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

$$RDDR = [36.8342 \text{ mL/min} / 13{,}800 \text{ mL/min}] \times [0.0898 / 0.129] \times [543{,}200 \text{ cm}^2 / 503.5 \text{ cm}^2] = 2.004$$

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

$$POD_{HEC} = POD_{ADJ} \times RDDR = 2.223 \text{ mg/m}^3 \times 2.004 = 4.46 \text{ mg/m}^3$$

# Appendix 3. MPPD Program Outputs for Supporting Studies

## *MPPD Program Output - Lee et al. (2003)*

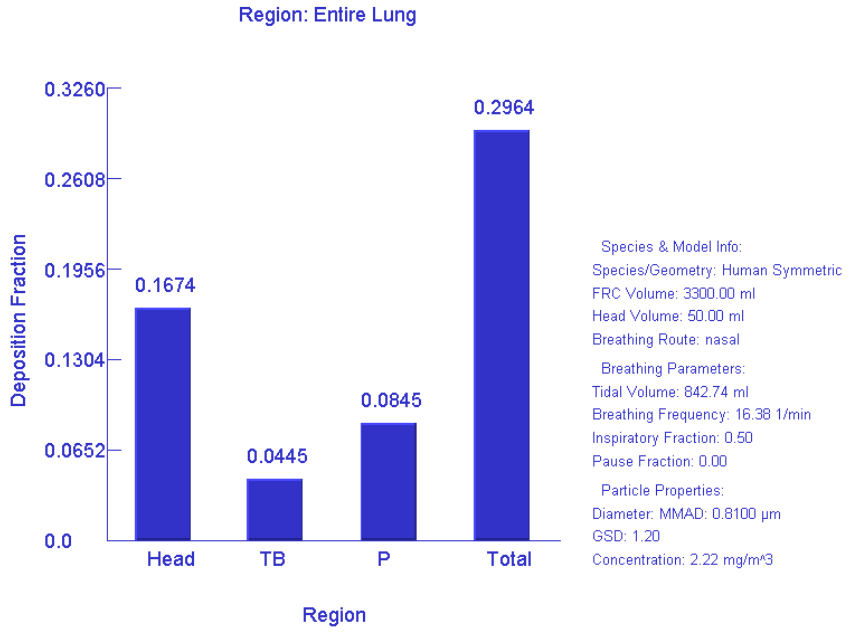


**Figure 7. Human output from the MPPD model from Lee et al. (2003)**

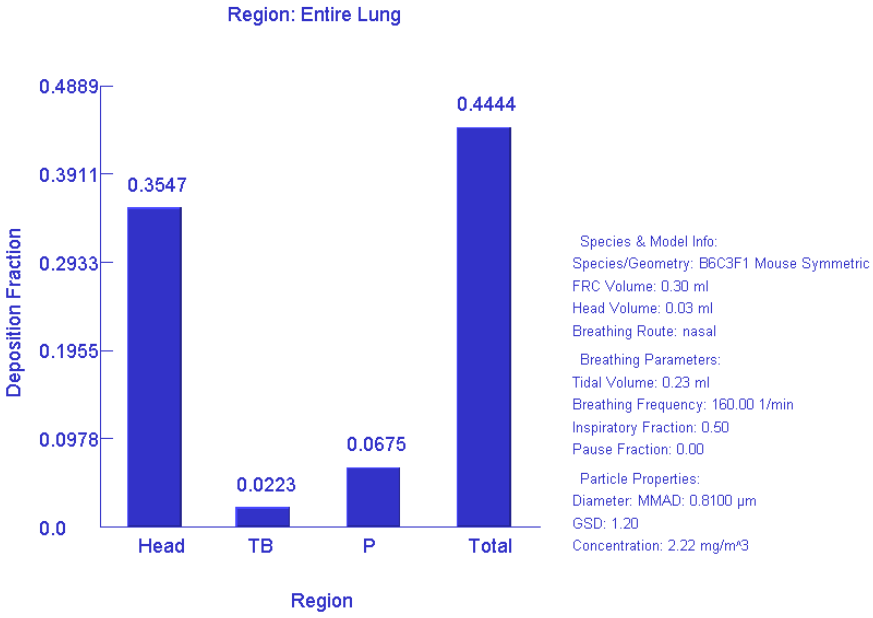


**Figure 8. Mouse output from the MPPD model from Lee et al. (2003)**

# Appendix 4. Benchmark Concentration Modeling

## *4.1 BMDS Summary of macrophage accumulation in the lungs of male rats*

**Table 25. Summary of BMD Modeling Results for Macrophage Accumulation in the Lungs of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.635 | 106.72 | 0.363 | 0.240 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 2° model was selected based on the lowest AIC. |
| Dichotomous-Hill | 0.0794 | 111.75 | 0.816 | 0.360 | |
| Logistic | 0.423 | 108.05 | 0.579 | 0.474 | |
| LogLogistic | 0.0794 | 111.75 | 0.814 | 0.360 | |
| Probit | 0.475 | 107.70 | 0.532 | 0.433 | |
| LogProbit | 0.0794 | 111.75 | 0.757 | 0.373 | |
| Weibull | 0.860 | 105.89 | 0.362 | 0.242 | |
| Multistage 3° | 0.993 | 107.52 | 0.349 | 0.201 | |
| **Multistage 2°** | **0.997** | **105.53** | **0.350** | **0.217** | |
| Quantal-Linear | 0.181 | 111.01 | 0.195 | 0.154 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, 0.03, -0.02, 0.07, respectively.

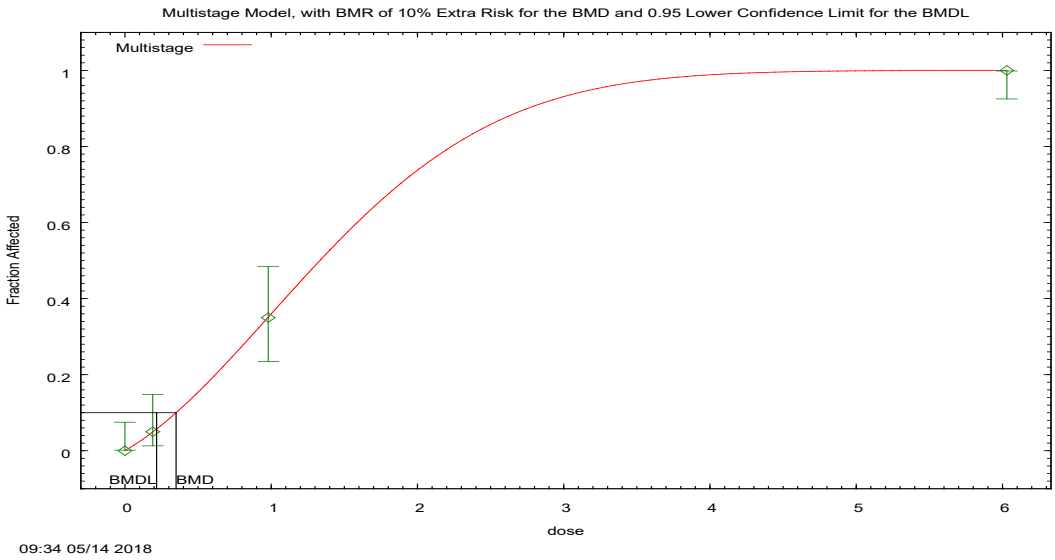


**Figure 9. Plot of incidence rate by dose with fitted curve for Multistage 2° model for macrophage accumulation in the lungs of male rats; dose shown in mg/m$^3$.**
**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 0.349813

BMDL at the 95% confidence level = 0.216585

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0 | 0 |
| Beta(1) | 0.223273 | 0 |
| Beta(2) | 0.222741 | 2.7739E+18 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -50.76 | 4 | | | |
| Fitted model | -50.76 | 2 | 0.0107018 | 2 | 0.99 |
| Reduced model | -155.39 | 1 | 209.259 | 3 | <.0001 |

AIC: = 105.526

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 60 | 0 |
| 0.19 | 0.0492 | 2.953 | 3 | 60 | 0.03 |
| 0.98 | 0.3513 | 21.076 | 21 | 60 | -0.02 |
| 6.03 | 0.9999 | 59.995 | 60 | 60 | 0.07 |

Chi^2 = 0.01 d.f. = 2 P-value = 0.997

## *4.2 BMDS Summary of macrophage accumulation in the lungs of female rats*

**Table 26. Summary of BMD Modeling Results for Macrophage Accumulation in the Lungs of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.983 | 94.113 | 0.449 | 0.308 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 2° model was selected based on the lowest AIC. |
| Dichotomous-Hill[b] | 0.319 | 97.430 | 0.744 | 0.387 | |
| Logistic | 0.814 | 94.702 | 0.647 | 0.523 | |
| LogLogistic[c] | 0.319 | 97.430 | 0.744 | 0.387 | |
| Probit | 0.863 | 94.526 | 0.588 | 0.473 | |
| LogProbit | 0.319 | 97.431 | 0.720 | 0.356 | |
| Weibull | 1.000 | 94.053 | 0.466 | 0.300 | |
| Multistage 3° | 1.000 | 96.053 | 0.472 | 0.303 | |
| **Multistage 2°** | **1.000** | **92.059** | **0.458** | **0.303** | |
| Quantal-Linear | 0.0707 | 103.47 | 0.193 | 0.153 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, -0.08, 0.02, 0, respectively.
[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

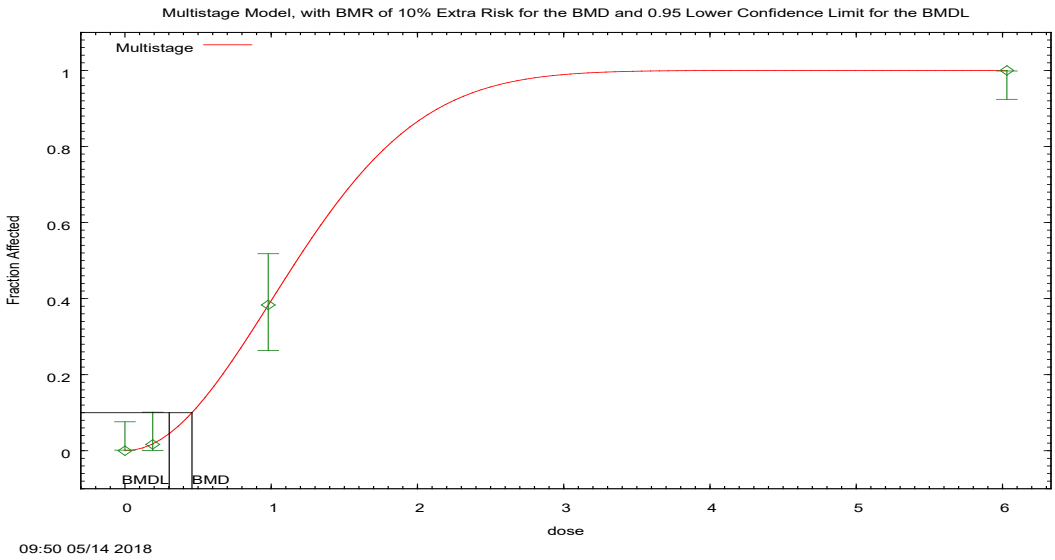


**Figure 10. Plot of incidence rate by dose with fitted curve for Multistage 2° model for macrophage accumulation in the lungs of female rats; dose shown in mg/m$^3$. Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 0.458296

BMDL at the 95% confidence level = 0.302671

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0 | 0 |
| Beta(1) | 0 | 0 |
| Beta(2) | 0.501632 | 2.7739E+18 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -45.03 | 4 | | | |
| Fitted model | -45.03 | 1 | 0.00597409 | 3 | 1 |
| Reduced model | -153.91 | 1 | 217.759 | 3 | <.0001 |

AIC: = 92.0586

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 59 | 0 |
| 0.19 | 0.0179 | 1.077 | 1 | 60 | -0.08 |
| 0.98 | 0.3823 | 22.939 | 23 | 60 | 0.02 |
| 6.03 | 1 | 59 | 59 | 59 | 0 |

Chi^2 = 0.01 d.f. = 3 P-value = 0.9999

## *4.3 BMDS Summary of macrophage accumulation in the lungs of combined rats*

**Table 27. Summary of BMD Modeling Results for Macrophage Accumulation in the Lungs of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.744 | 197.66 | 0.397 | 0.305 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 2° model was selected based on the lowest AIC. |
| Dichotomous-Hill[b] | 0.0446 | 204.37 | 0.784 | 0.422 | |
| Logistic | 0.366 | 199.84 | 0.604 | 0.524 | |
| LogLogistic[c] | 0.0446 | 204.37 | 0.784 | 0.422 | |
| Probit | 0.442 | 199.28 | 0.551 | 0.477 | |
| LogProbit | 0.0446 | 204.37 | 0.740 | 0.440 | |
| Weibull | 0.985 | 196.84 | 0.394 | 0.298 | |
| Multistage 3° | 1.000 | 198.79 | 0.420 | 0.279 | |
| **Multistage 2°** | **1.000** | **196.79** | **0.408** | **0.281** | |
| Quantal-Linear | 0.0097 | 212.48 | 0.194 | 0.165 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, 0, 0, 0.01, respectively.
[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

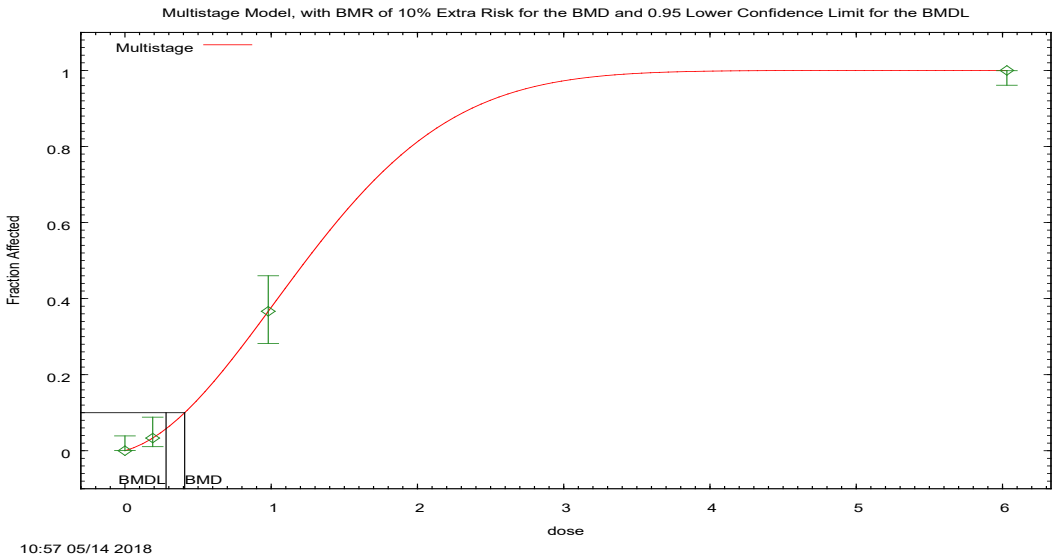


**Figure 11. Plot of incidence rate by dose with fitted curve for Multistage 2° model for macrophage accumulation in the lungs of combined rats; dose shown in mg/m$^3$. Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 0.408449

BMDL at the 95% confidence level = 0.281176

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0 | 0 |
| Beta(1) | 0.1092 | 0 |
| Beta(2) | 0.364188 | 2.7739E+18 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -96.4 | 4 | | | |
| Fitted model | -96.4 | 2 | 0.000218827 | 2 | 1 |
| Reduced model | -309.29 | 1 | 425.794 | 3 | <.0001 |

AIC: = 196.793

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 119 | 0 |
| 0.19 | 0.0333 | 3.999 | 4 | 120 | 0 |
| 0.98 | 0.3667 | 44.002 | 44 | 120 | 0 |
| 6.03 | 1 | 119 | 119 | 119 | 0.01 |

Chi^2 = 0 d.f. = 2 P-value = 0.9999

## *4.4 BMDS Summary of alveolar duct epithelialization in the lungs of male rats*

**Table 28. Summary of BMD Modeling Results for Alveolar Duct Epithelialization in the Lungs of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.250 | 104.32 | 0.910 | 0.630 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC. |
| Dichotomous-Hill | N/A[b] | 105.70 | 0.954 | 0.674 | |
| Logistic | 0.0568 | 107.77 | 1.61 | 1.27 | |
| LogLogistic | 0.274 | 104.09 | 0.898 | 0.657 | |
| Probit | 0.0916 | 106.64 | 1.45 | 1.18 | |
| **LogProbit** | **0.310** | **103.75** | **0.890** | **0.660** | |
| Weibull | 0.211 | 104.78 | 0.920 | 0.614 | |
| Multistage 3°[c] | 0.153 | 105.54 | 0.977 | 0.596 | |
| Multistage 2°[d] | 0.153 | 105.54 | 0.977 | 0.596 | |
| Quantal-Linear | 0.0034 | 115.97 | 0.379 | 0.302 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.7, -0.73, 0.04, -0.02, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] The Multistage 3° model may appear equivalent to the Multistage 2° model, however differences exist in digits not displayed in the table.
[d] The Multistage 2° model may appear equivalent to the Multistage 3° model, however differences exist in digits not displayed in the table.

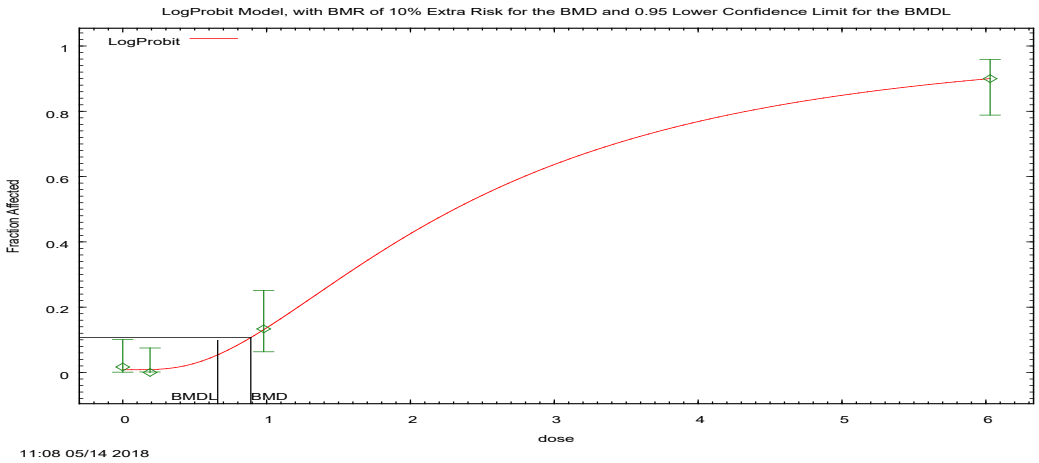


**Figure 12. Plot of incidence rate by dose with fitted curve for LogProbit model for alveolar duct epithelialization in the lungs of male rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.890376

BMDL at the 95% confidence level = 0.660056

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.00837975 | 0.0166667 |
| intercept | -1.1260E+00 | -8.1116E-01 |
| slope | 1.33944 | 1.06719 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -48.15 | 4 | | | |
| Fitted model | -48.87 | 3 | 1.44472 | 1 | 0.23 |
| Reduced model | -138.16 | 1 | 180.012 | 3 | <.0001 |

AIC: = 103.748

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|---|---|---|---|---|---|
| 0 | 0.0084 | 0.503 | 1 | 60 | 0.7 |
| 0.19 | 0.0088 | 0.527 | 0 | 60 | -0.73 |
| 0.98 | 0.1318 | 7.906 | 8 | 60 | 0.04 |
| 6.03 | 0.9007 | 54.041 | 54 | 60 | -0.02 |

Chi^2 = 1.03 d.f. = 1 P-value = 0.3104

## *4.5 BMDS Summary of alveolar duct epithelialization in the lungs of female rats*

**Table 29. Summary of BMD Modeling Results for Alveolar Duct Epithelialization in the Lungs of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.910 | 68.937 | 0.874 | 0.640 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC. |
| Dichotomous-Hill | 1.000 | 70.590 | 0.950 | 0.698 | |
| Logistic | 0.0366 | 77.684 | 1.43 | 1.10 | |
| LogLogistic | 0.960 | 68.749 | 0.883 | 0.692 | |
| Probit | 0.0573 | 76.278 | 1.35 | 1.07 | |
| **LogProbit** | **0.998** | **68.600** | **0.883** | **0.693** | |
| Weibull | 0.783 | 69.478 | 0.875 | 0.615 | |
| Multistage 3°[b] Multistage 2° | 0.630 | 69.993 | 0.931 | 0.610 | |
| Quantal-Linear | 0.0016 | 88.454 | 0.318 | 0.253 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, -0.07, 0.01, -0.01, respectively.
[b] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

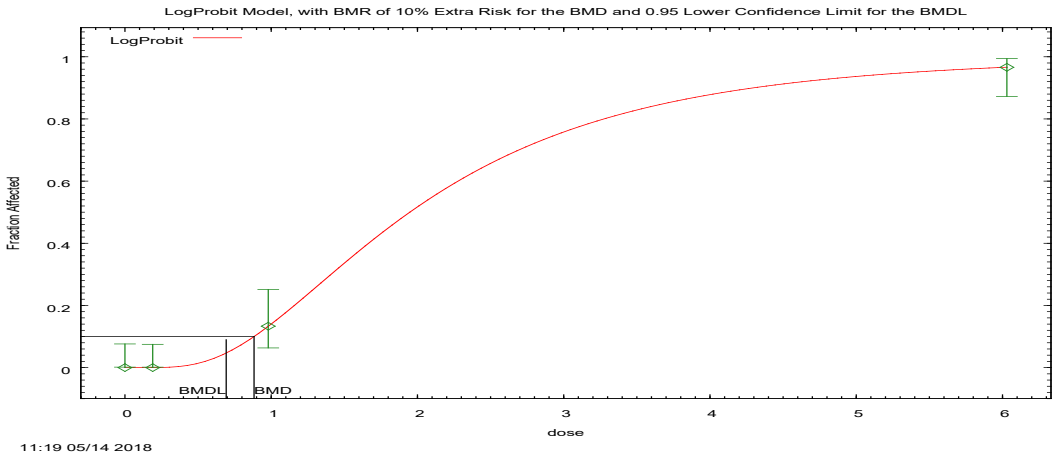


**Figure 13. Plot of incidence rate by dose with fitted curve for LogProbit model for alveolar duct epithelialization in the lungs of female rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.882708

BMDL at the 95% confidence level = 0.692508

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0 | 0 |
| intercept | -1.0797E+00 | -6.1018E-01 |
| slope | 1.61835 | 1.22831 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -32.3 | 4 | | | |
| Fitted model | -32.3 | 2 | 0.00999311 | 2 | 1 |
| Reduced model | -139.55 | 1 | 214.502 | 3 | <.0001 |

AIC: = 68.5999

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 59 | 0 |
| 0.19 | 0.0001 | 0.005 | 0 | 60 | -0.07 |
| 0.98 | 0.133 | 7.98 | 8 | 60 | 0.01 |
| 6.03 | 0.9662 | 57.008 | 57 | 59 | -0.01 |

Chi^2 = 0.01  d.f. = 2  P-value = 0.9975

## *4.6 BMDS Summary of alveolar duct epithelialization in the lungs of combined rats*

**Table 30. Summary of BMD Modeling Results for Alveolar Duct Epithelialization in the Lungs of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | ***p*-value** | **AIC** | | | |
| Gamma | 0.214 | 172.85 | 0.890 | 0.704 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC. |
| Dichotomous-Hill | N/A[b] | 173.84 | 0.952 | 0.747 | |
| Logistic | 0.0021 | 184.14 | 1.54 | 1.30 | |
| LogLogistic | 0.255 | 172.40 | 0.887 | 0.730 | |
| Probit | 0.0057 | 181.55 | 1.41 | 1.21 | |
| **LogProbit** | **0.308** | **171.89** | **0.884** | **0.732** | |
| Weibull | 0.148 | 173.85 | 0.896 | 0.688 | |
| Multistage 3°[c] Multistage 2° | 0.0808 | 175.27 | 0.951 | 0.692 | |
| Quantal-Linear | 0 | 204.54 | 0.348 | 0.296 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.71, -0.73, 0.03, -0.02, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

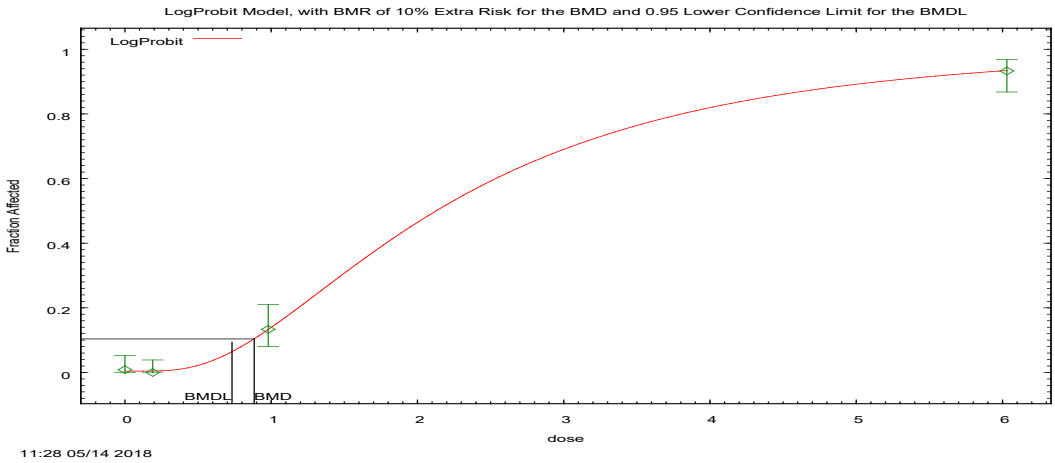


**Figure 14. Plot of incidence rate by dose with fitted curve for LogProbit model for alveolar duct epithelialization in the lungs of combined rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.883873

BMDL at the 95% confidence level = 0.732277

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.00419756 | 0.00840336 |
| intercept | -1.1029E+00 | -8.1147E-01 |
| slope | 1.44727 | 1.19973 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -82.22 | 4 | | | |
| Fitted model | -82.95 | 3 | 1.45452 | 1 | 0.23 |
| Reduced model | -277.74 | 1 | 391.039 | 3 | <.0001 |

AIC: = 171.891

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0042 | 0.5 | 1 | 119 | 0.71 |
| 0.19 | 0.0044 | 0.531 | 0 | 120 | -0.73 |
| 0.98 | 0.1324 | 15.893 | 16 | 120 | 0.03 |
| 6.03 | 0.9331 | 111.044 | 111 | 119 | -0.02 |

Chi^2 = 1.04 d.f. = 1 P-value = 0.3083

## *4.7 BMDS Summary of localized fibrosis in the lungs of male rats*

**Table 31. Summary of BMD Modeling Results for Localized Fibrosis in the Lungs of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.154 | 139.67 | 0.882 | 0.552 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC. |
| Dichotomous-Hill | N/A[b] | 139.88 | 0.940 | 0.621 | |
| Logistic | 0.0136 | 144.81 | 1.91 | 1.56 | |
| LogLogistic | 0.190 | 139.20 | 0.849 | 0.558 | |
| Probit | 0.0223 | 143.67 | 1.71 | 1.41 | |
| **LogProbit** | **0.263** | **138.37** | **0.829** | **0.563** | |
| Weibull | 0.139 | 139.97 | 0.877 | 0.537 | |
| Multistage 3° | 0.107 | 140.78 | 0.866 | 0.498 | |
| Multistage 2° | 0.107 | 140.78 | 0.866 | 0.499 | |
| Quantal-Linear | 0.124 | 141.18 | 0.542 | 0.429 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.67, -0.86, 0.25, -0.1, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.

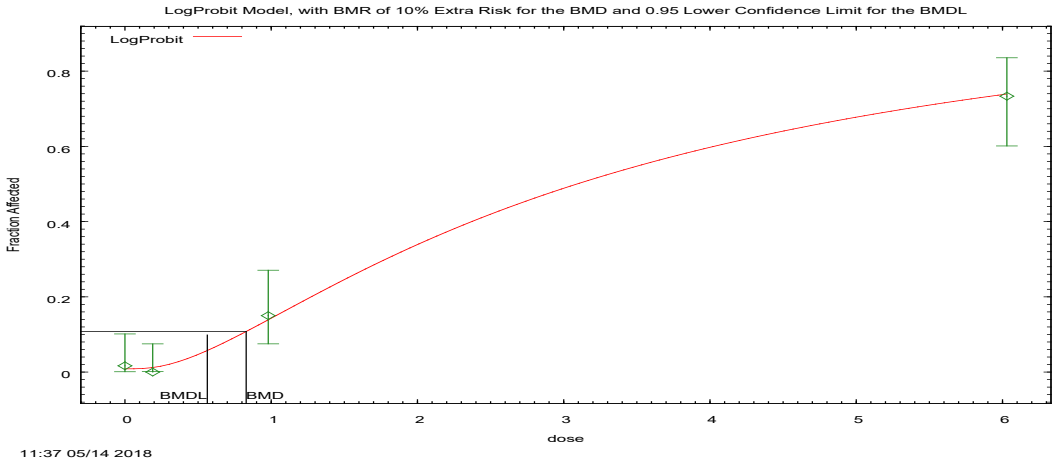


**Figure 15. Plot of incidence rate by dose with fitted curve for LogProbit model for localized fibrosis in the lungs of male rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.82908

BMDL at the 95% confidence level = 0.563251

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.00864842 | 0.0166667 |
| intercept | -1.1007E+00 | -9.9736E-01 |
| slope | 0.964908 | 0.871624 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -65.24 | 4 | | | |
| Fitted model | -66.18 | 3 | 1.87983 | 1 | 0.17 |
| Reduced model | -127.96 | 1 | 125.432 | 3 | <.0001 |

AIC: = 138.367

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0086 | 0.519 | 1 | 60 | 0.67 |
| 0.19 | 0.0121 | 0.723 | 0 | 60 | -0.86 |
| 0.98 | 0.1388 | 8.33 | 9 | 60 | 0.25 |
| 6.03 | 0.7389 | 44.335 | 44 | 60 | -0.1 |

Chi^2 = 1.25 d.f. = 1 P-value = 0.2627

## *4.8 BMDS Summary of localized fibrosis in the lungs of female rats*

**Table 32. Summary of BMD Modeling Results for Localized Fibrosis in the Lungs of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.942 | 90.372 | 1.25 | 0.868 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC/BMCL. |
| Dichotomous-Hill | 1.000 | 92.152 | 1.03 | 0.871 | |
| Logistic | 0.145 | 95.261 | 2.33 | 1.84 | |
| LogLogistic | 0.949 | 90.350 | 1.21 | 0.862 | |
| Probit | 0.217 | 94.244 | 2.04 | 1.64 | |
| **LogProbit** | **0.996** | **90.167** | **1.16** | **0.852** | |
| Weibull | 0.891 | 90.573 | 1.31 | 0.873 | |
| Multistage 3°[b] Multistage 2° | 0.806 | 90.821 | 1.39 | 0.911 | |
| Quantal-Linear | 0.0130 | 102.94 | 0.506 | 0.400 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, -0.09, 0.01, 0, respectively.
[b] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

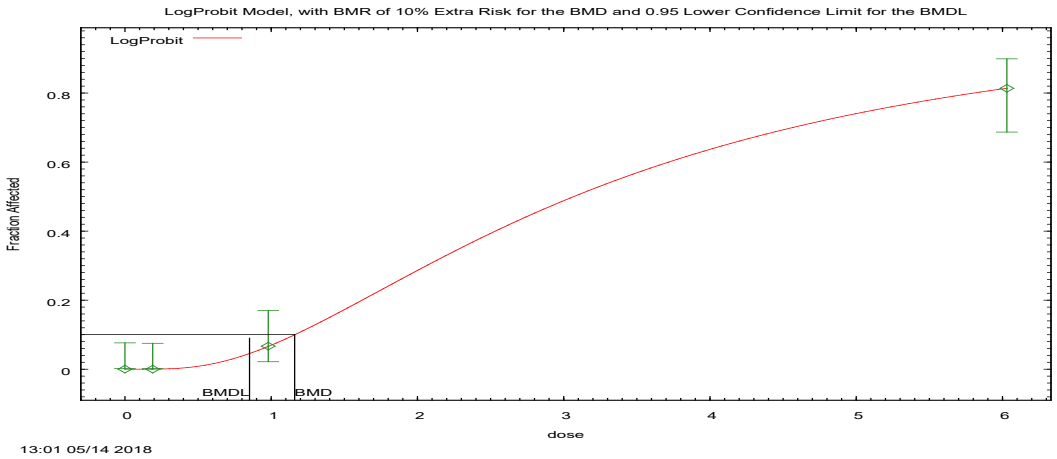


**Figure 16. Plot of incidence rate by dose with fitted curve for LogProbit model for localized fibrosis in the lungs of female rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 1.16045

BMDL at the 95% confidence level = 0.852014

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0 | 0 |
| intercept | -1.4778E+00 | -1.0415E+00 |
| slope | 1.31896 | 0.95736 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -43.08 | 4 | | | |
| Fitted model | -43.08 | 2 | 0.0148616 | 2 | 0.99 |
| Reduced model | -124.95 | 1 | 163.742 | 3 | <.0001 |

AIC: = 90.1669

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 59 | 0 |
| 0.19 | 0.0001 | 0.007 | 0 | 60 | -0.09 |
| 0.98 | 0.0662 | 3.974 | 4 | 60 | 0.01 |
| 6.03 | 0.8138 | 48.015 | 48 | 59 | 0 |

Chi^2 = 0.01 d.f. = 2 P-value = 0.9962

## *4.9 BMDS Summary of localized fibrosis in the lungs of combined rats*

**Table 33. Summary of BMD Modeling Results for Localized Fibrosis in the Lungs of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.173 | 230.27 | 1.04 | 0.785 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC/BMCL. |
| Dichotomous-Hill | N/A[b] | 230.72 | 0.975 | 0.807 | |
| Logistic | 0.0027 | 239.67 | 2.07 | 1.77 | |
| LogLogistic | 0.201 | 229.92 | 1.01 | 0.775 | |
| Probit | 0.0071 | 237.47 | 1.83 | 1.58 | |
| **LogProbit** | **0.288** | **228.97** | **0.974** | **0.766** | |
| Weibull | 0.139 | 230.88 | 1.06 | 0.780 | |
| Multistage 3°[c]<br>Multistage 2° | 0.0828 | 232.26 | 1.12 | 0.776 | |
| Quantal-Linear | 0.0015 | 243.76 | 0.523 | 0.443 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.7, -0.79, 0.12, -0.04, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

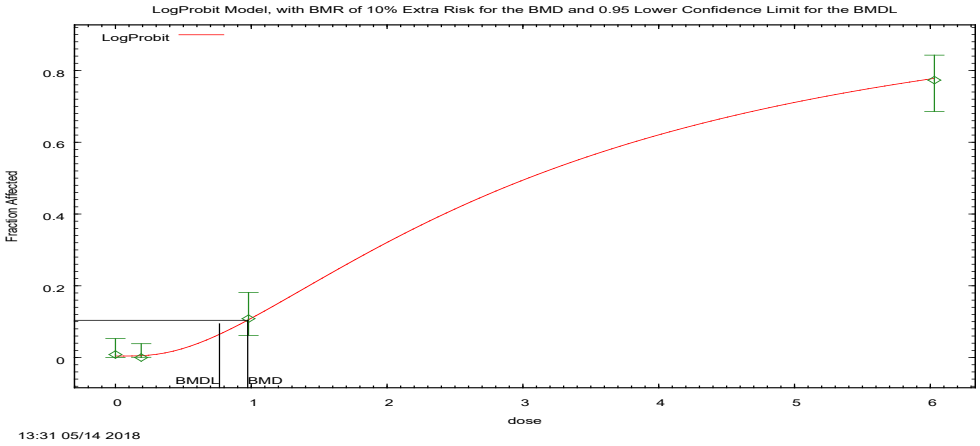


**Figure 17. Plot of incidence rate by dose with fitted curve for LogProbit model for localized fibrosis in the lungs of combined rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.973834

BMDL at the 95% confidence level = 0.766116

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.00424583 | 0.00840336 |
| intercept | -1.2520E+00 | -1.0966E+00 |
| slope | 1.11513 | 0.980886 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -110.66 | 4 | | | |
| Fitted model | -111.48 | 3 | 1.64399 | 1 | 0.2 |
| Reduced model | -252.92 | 1 | 284.521 | 3 | <.0001 |

AIC: = 228.965

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0042 | 0.505 | 1 | 119 | 0.7 |
| 0.19 | 0.0052 | 0.624 | 0 | 120 | -0.79 |
| 0.98 | 0.1051 | 12.607 | 13 | 120 | 0.12 |
| 6.03 | 0.7748 | 92.204 | 92 | 119 | -0.04 |

Chi^2 = 1.13 d.f. = 1 P-value = 0.288

## *4.10 BMDS Summary of Bowman's gland hyperplasia in the nasal cavity of male rats*

**Table 34. Summary of BMD Modeling Results for Bowman's Gland Hyperplasia in the Nasal Cavity of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma[b]<br>Multistage 3°[c]<br>Multistage 2°[d] | 0.0421 | 150.16 | 1.60 | 1.10 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogProbit model was selected based on the lowest AIC/BMCL. |
| Dichotomous-Hill | 1.000 | 145.79 | 0.572 | 0.304 | |
| Logistic | 0.0070 | 155.27 | 3.40 | 2.75 | |
| LogLogistic | 0.0792 | 148.75 | 1.26 | 0.824 | |
| Probit | 0.0081 | 154.86 | 3.18 | 2.54 | |
| **LogProbit** | **0.759** | **144.34** | **0.661** | **0.239** | |
| Weibull[e]<br>Quantal-Linear[f] | 0.0421 | 150.16 | 1.60 | 1.10 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0, -0.41, 0.57, -0.22, respectively.
[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[c] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[d] The Multistage 2° model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[e] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[f] The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model.

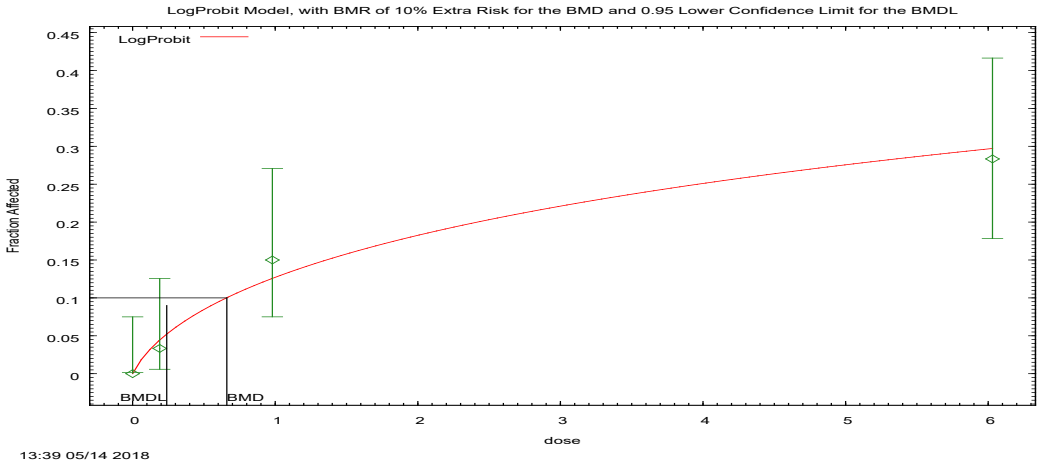


**Figure 18. Plot of incidence rate by dose with fitted curve for LogProbit model for Bowman's gland hyperplasia in the nasal cavity of male rats; dose shown in mg/m$^3$.**
**Probit Model.** (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.660574

BMDL at the 95% confidence level = 0.239356

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0 | 0 |
| intercept | -1.1414E+00 | -1.1618E+00 |
| slope | 0.337902 | 0.362743 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -69.9 | 4 | | | |
| Fitted model | -70.17 | 2 | 0.550648 | 2 | 0.76 |
| Reduced model | -86.46 | 1 | 33.1193 | 3 | <.0001 |

AIC: = 144.342

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 60 | 0 |
| 0.19 | 0.0443 | 2.659 | 2 | 60 | -0.41 |
| 0.98 | 0.1254 | 7.526 | 9 | 60 | 0.57 |
| 6.03 | 0.2966 | 17.794 | 17 | 60 | -0.22 |

Chi^2 = 0.55  d.f = 2  P-value = 0.759

## *4.11 BMDS Summary of Bowman's gland hyperplasia in the nasal cavity of female rats*

**Table 35. Summary of BMD Modeling Results for Bowman's Gland Hyperplasia in the Nasal Cavity of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | ***p*-value** | **AIC** | | | |
| Gamma | 0.0180 | 162.30 | 603 | 2.57 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogLogistic model was selected based on the lowest AIC/BMDL. |
| Dichotomous-Hill | N/A[b] | 158.50 | 0.418 | 0.180 | |
| Logistic | 0.178 | 158.33 | 8.41 | 4.27 | |
| **LogLogistic** | **0.188** | **158.15** | **8.31** | **2.98** | |
| Probit | 0.179 | 158.31 | 8.44 | 4.13 | |
| LogProbit | 0.732 | 156.62 | 2.20 | error[c] | |
| Weibull[d]<br>Quantal-Linear[e] | 0.187 | 158.18 | 8.36 | 3.20 | |
| Multistage 3°[f]<br>Multistage 2°[g] | 0.187 | 158.18 | 8.36 | 3.20 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -1.33, 0.5, 1.11, -0.28, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.
[d] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[e] The Quantal-Linear model may appear equivalent to the Multistage 3° model, however differences exist in digits not displayed in the table. This also applies to the Multistage 2° model.
[f] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[g] The Multistage 2° model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.

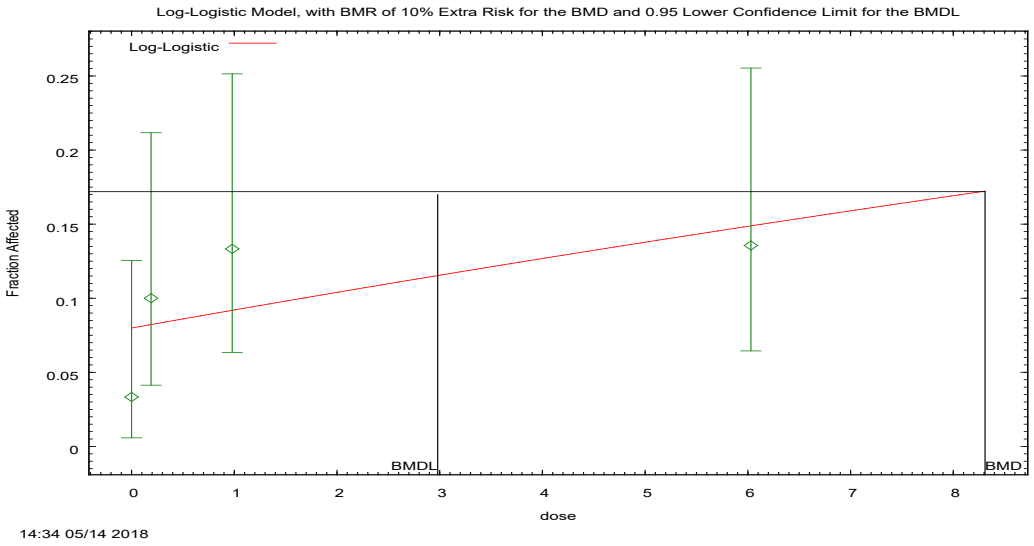


**Figure 19. Plot of incidence rate by dose with fitted curve for LogLogistic model for Bowman's gland hyperplasia in the nasal cavity of female rats; dose shown in mg/m$^3$.**
**Logistic Model.** (Version: 2.15; Date: 3/20/2017)

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 = 8.3094

BMDL at the 95% confidence level = 2.98018

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.0798976 | 0.0333333 |
| intercept | -4.3146E+00 | -3.2606E+00 |
| slope | 1 | 1 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -75.25 | 4 | | | |
| Fitted model | -77.08 | 2 | 3.65016 | 2 | 0.16 |
| Reduced model | -77.91 | 1 | 5.32824 | 3 | 0.15 |

AIC: = 158.151

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0799 | 4.794 | 2 | 60 | -1.33 |
| 0.19 | 0.0822 | 4.934 | 6 | 60 | 0.5 |
| 0.98 | 0.0918 | 5.508 | 8 | 60 | 1.11 |
| 6.03 | 0.1486 | 8.765 | 8 | 59 | -0.28 |

Chi^2 = 3.34 d.f. = 2 P-value = 0.1882

## *4.12 BMDS Summary of Bowman's gland hyperplasia in the nasal cavity of combined rats*

**Table 36. Summary of BMD Modeling Results for Bowman's Gland Hyperplasia in the Nasal Cavity of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma[b] | 0.0136 | 312.33 | 2.94 | 1.98 | Of the models that provided an adequate fit and a valid BMDL estimate, the Dichotomous-Hill model was selected based on the lowest AIC. |
| **Dichotomous-Hill** | **0.899** | **305.41** | **0.560** | **0.331** | |
| Logistic | 0.0047 | 314.99 | 4.30 | 3.43 | |
| LogLogistic | 0.0175 | 311.76 | 2.65 | 1.70 | |
| Probit | 0.0053 | 314.71 | 4.14 | 3.24 | |
| LogProbit | 0.540 | 305.76 | 0.711 | 0.185 | |
| Weibull[c]<br>Multistage 3°[d]<br>Multistage 2°[e]<br>Quantal-Linear[f] | 0.0136 | 312.33 | 2.94 | 1.98 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -0.02, 0.08, -0.09, 0.04, respectively.
[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model. This also applies to the Quantal-Linear model.
[c] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[e] The Multistage 2° model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table.
[f] The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table.

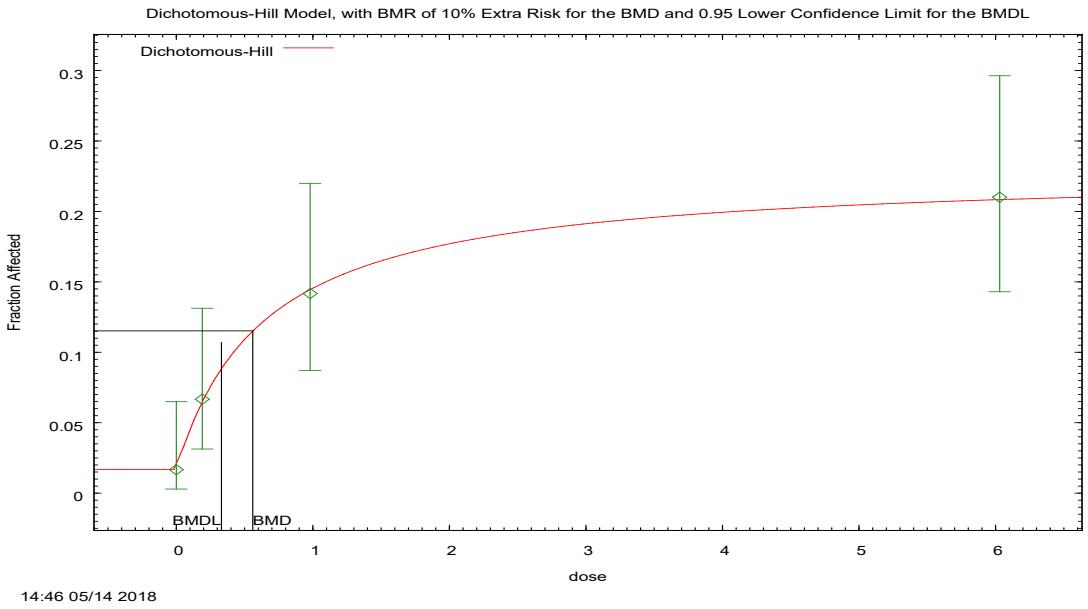


**Figure 20. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Bowman's gland hyperplasia in the nasal cavity of combined rats; dose shown in mg/m$^3$. Dichotomous Hill Model.** (Version: 1.3; Date: 02/28/2013)

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

Slope parameter is restricted as slope >= 1

**Warning: BMDL computation is at best imprecise for these data**

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.559769

BMDL at the 95% confidence level = 0.330538

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| v | 0.229271 | 1 |
| g | 0.0736493 | 0.0166667 |
| intercept | 0.431528 | -2.7253E+00 |
| slope | 1 | 1 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -149.7 | 4 | | | |
| Fitted model | -149.7 | 3 | 0.0161323 | 1 | 0.9 |
| Reduced model | -164.53 | 1 | 29.6764 | 3 | <.0001 |

AIC: = 305.406

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0169 | 2.026 | 2 | 120 | -0.02 |
| 0.19 | 0.065 | 7.794 | 8 | 120 | 0.08 |
| 0.98 | 0.1446 | 17.354 | 17 | 120 | -0.09 |
| 6.03 | 0.2086 | 24.826 | 25 | 119 | 0.04 |

Chi^2 = 0.02 d.f. = 1 P-value = 0.8989

## *4.13 BMDS Summary of basal cell hyperplasia in the nasal cavity of male rats*

**Table 37. Summary of BMD Modeling Results for Basal Cell Hyperplasia in the Nasal Cavity of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma[b]<br>Weibull[c]<br>Multistage 3°[d]<br>Multistage 2°<br>Quantal-Linear | 0.0877 | 301.67 | 1.21 | 0.778 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogLogistic model was selected based on the lowest AIC. |
| Dichotomous-Hill | N/A[e] | 300.98 | 0.795 | 0.644 | |
| Logistic | 0.0545 | 302.61 | 1.74 | 1.28 | |
| **LogLogistic** | **0.132** | **300.88** | **0.879** | **0.485** | |
| Probit | 0.0563 | 302.54 | 1.70 | 1.25 | |
| LogProbit | 0.142 | 301.11 | 0.308 | 0.0304 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -0.26, -0.85, 1.69, -0.62, respectively.
[b] For the Gamma and Weibull models, the power parameter estimates were 1 (boundary of parameter space). For the Gamma model, the power parameter estimate was 1. The model is equivalent to the Quantal-Linear model.
[c] For the Weibull and Gamma models, the power parameter estimates were 1 (boundary of parameter space). For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[e] No available degrees of freedom to calculate a goodness of fit value.

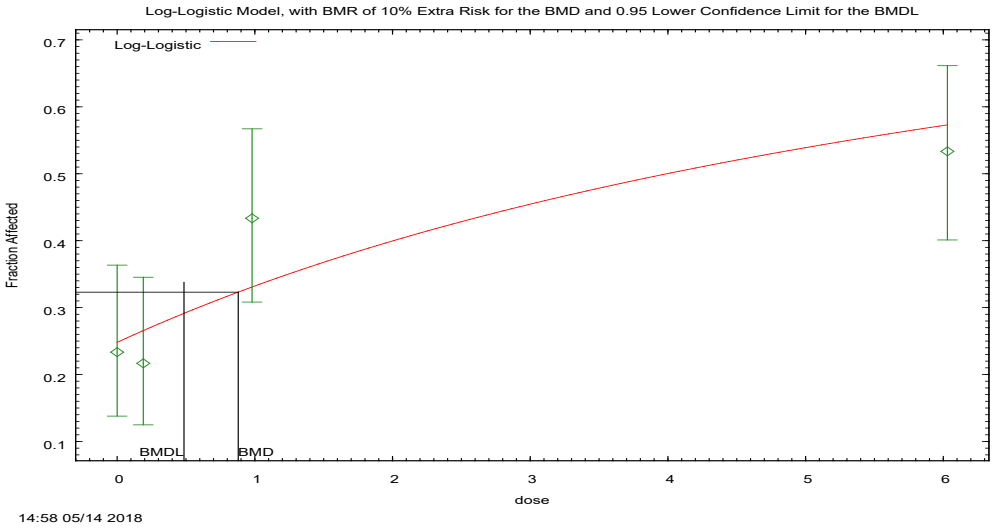


**Figure 21. Plot of incidence rate by dose with fitted curve for LogLogistic model for basal cell hyperplasia in the nasal cavity of male rats; dose shown in mg/m$^3$.**
**Logistic Model.** (Version: 2.15; Date: 3/20/2017)

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 = 0.879418

BMDL at the 95% confidence level = 0.485377

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.247714 | 0.233333 |
| intercept | -2.0687E+00 | -2.1410E+00 |
| slope | 1 | 1.24269 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -146.46 | 4 | | | |
| Fitted model | -148.44 | 2 | 3.95422 | 2 | 0.14 |
| Reduced model | -156 | 1 | 19.0641 | 3 | 0 |

AIC: = 300.884

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.2477 | 14.863 | 14 | 60 | -0.26 |
| 0.19 | 0.2654 | 15.921 | 13 | 60 | -0.85 |
| 0.98 | 0.3306 | 19.836 | 26 | 60 | 1.69 |
| 6.03 | 0.573 | 34.381 | 32 | 60 | -0.62 |

Chi^2 = 4.04 d.f. = 2 P-value = 0.1324

## *4.14 BMDS Summary of basal cell hyperplasia in the nasal cavity of female rats*

**Table 38. Summary of BMD Modeling Results for Basal Cell Hyperplasia in the Nasal Cavity of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.225 | 184.82 | 1.47 | 0.672 | Of the models that provided an adequate fit and a valid BMDL estimate, the Logistic model was selected based on the lowest AIC. |
| Dichotomous-Hill[b] | 0.226 | 184.82 | 1.45 | 0.758 | |
| **Logistic** | **0.501** | **182.66** | **1.27** | **1.03** | |
| LogLogistic[c] | 0.226 | 184.82 | 1.45 | 0.758 | |
| Probit | 0.473 | 182.76 | 1.16 | 0.969 | |
| LogProbit | 0.224 | 184.84 | 1.38 | 0.815 | |
| Weibull | 0.230 | 184.78 | 1.52 | 0.642 | |
| Multistage 3° | 0.273 | 184.51 | 1.54 | 0.566 | |
| Multistage 2° | 0.232 | 184.74 | 1.37 | 0.573 | |
| Quantal-Linear | 0.0404 | 188.46 | 0.442 | 0.345 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -0.55, 0.96, -0.4, 0.04, respectively.
[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

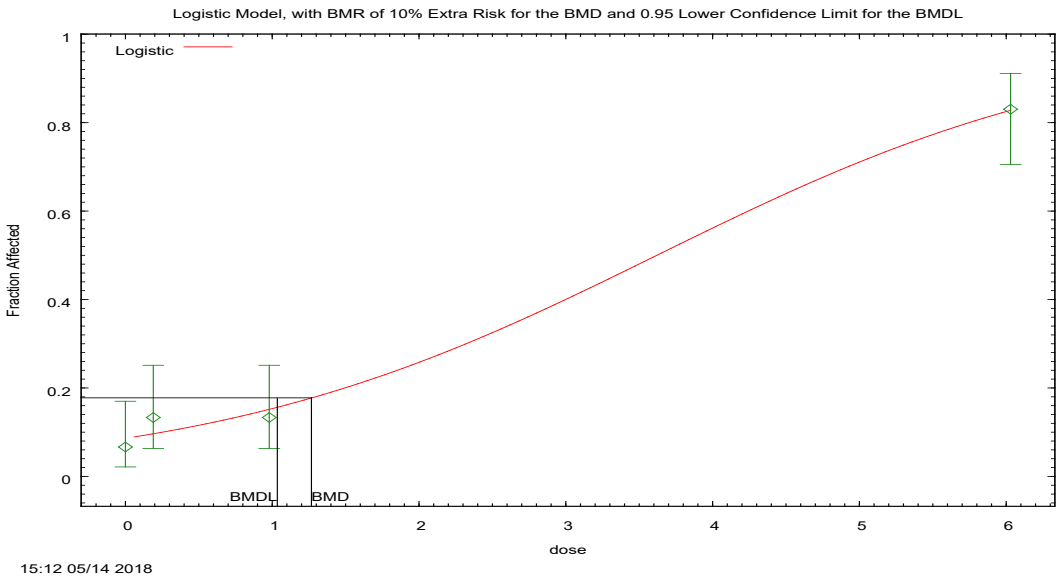


**Figure 22. Plot of incidence rate by dose with fitted curve for Logistic model for basal cell hyperplasia in the nasal cavity of female rats; dose shown in mg/m$^3$.**
**Logistic Model.** (Version: 2.15; Date: 3/20/2017)

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

Slope parameter is not restricted

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 1.26708

BMDL at the 95% confidence level = 1.03475

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | n/a | 0 |
| intercept | -2.3579E+00 | -2.3016E+00 |
| slope | 0.652338 | 0.63686 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -88.67 | 4 | | | |
| Fitted model | -89.33 | 2 | 1.32281 | 2 | 0.52 |
| Reduced model | -143.64 | 1 | 109.939 | 3 | <.0001 |

AIC: = 182.656

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0864 | 5.186 | 4 | 60 | -0.55 |
| 0.19 | 0.0967 | 5.804 | 8 | 60 | 0.96 |
| 0.98 | 0.152 | 9.123 | 8 | 60 | -0.4 |
| 6.03 | 0.8286 | 48.887 | 49 | 59 | 0.04 |

Chi^2 = 1.38 d.f. = 2 P-value = 0.5013

## *4.15 BMDS Summary of basal cell hyperplasia in the nasal cavity of combined rats*

**Table 39. Summary of BMD Modeling Results for Basal Cell Hyperplasia in the Nasal Cavity of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| **Gamma[b]** | **0.983** | **508.91** | **0.645** | **0.520** | Of the models that provided an adequate fit and a valid BMDL estimate, the Gamma model was selected based on the lowest AIC. The Weibull, Multistage, and Quantal-Linear models gave similar AIC/BMDL values. |
| Dichotomous-Hill | 0.934 | 510.88 | 0.639 | 0.340 | |
| Logistic | 0.356 | 510.92 | 1.26 | 1.10 | |
| LogLogistic | 0.934 | 510.88 | 0.639 | 0.338 | |
| Probit | 0.399 | 510.69 | 1.20 | 1.05 | |
| LogProbit | 0.765 | 510.97 | 0.680 | 0.314 | |
| Weibull[c] | 0.983 | 508.91 | 0.645 | 0.520 | |
| Multistage 3°[d]<br>Multistage 2°[e]<br>Quantal-Linear[f] | 0.983 | 508.91 | 0.645 | 0.520 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -0.04, -0.06, 0.16, -0.06, respectively.
[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model. This also applies to the Quantal-Linear model.
[c] The Weibull model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model. This also applies to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[e] The Multistage 2° model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Weibull model.
[f] The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Weibull model.

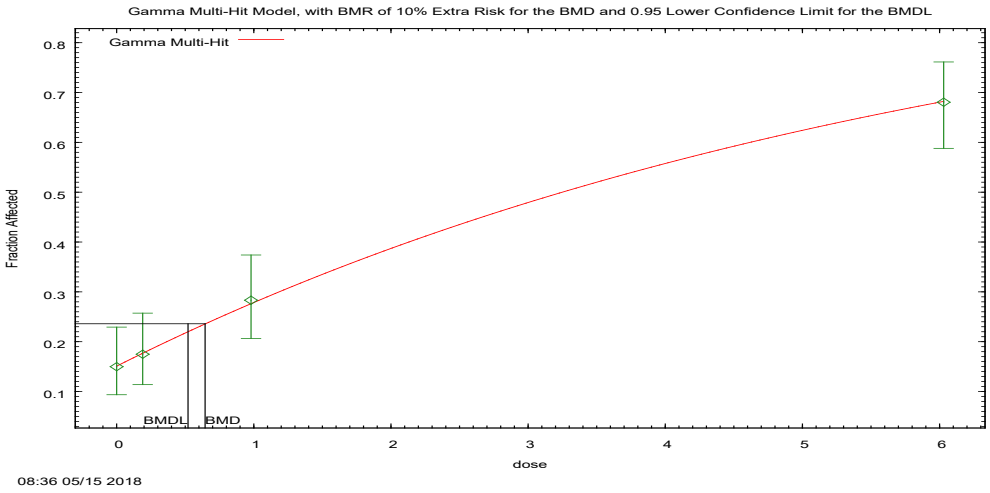


**Figure 23. Plot of incidence rate by dose with fitted curve for Gamma model for basal cell hyperplasia in the nasal cavity of combined rats; dose shown in mg/m$^3$.**
**Gamma Model.** (Version: 2.17; Date: 6/22/2017)

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

Power parameter is restricted as power >=1

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 0.644937

BMDL at the 95% confidence level = 0.52042

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0.151213 | 0.155738 |
| Slope | 0.163366 | 0.211314 |
| Power | 1 | 1.27207 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -252.44 | 4 | | | |
| Fitted model | -252.46 | 2 | 0.0339419 | 2 | 0.98 |
| Reduced model | -300.81 | 1 | 96.745 | 3 | <.0001 |

AIC: = 508.91

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.1512 | 18.146 | 18 | 120 | -0.04 |
| 0.19 | 0.1772 | 21.259 | 21 | 120 | -0.06 |
| 0.98 | 0.2768 | 33.214 | 34 | 120 | 0.16 |
| 6.03 | 0.6831 | 81.284 | 81 | 119 | -0.06 |

Chi^2 = 0.03 d.f = 2 P-value = 0.9831

## *4.16 BMDS Summary of olfactory epithelial degeneration in the nasal cavity of male rats*

**Table 40. Summary of BMD Modeling Results for Olfactory Epithelial Degeneration in the Nasal Cavity of Male Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma[b]<br>Multistage 3°[c]<br>Multistage 2°[d] | 0.374 | 244.66 | 1.48 | 0.973 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogLogistic model was selected based on the lowest AIC. |
| Dichotomous-Hill | 0.884 | 244.74 | 0.464 | 0.305 | |
| Logistic | 0.217 | 245.76 | 2.32 | 1.79 | |
| **LogLogistic** | **0.475** | **244.19** | **1.19** | **0.702** | |
| Probit | 0.230 | 245.64 | 2.21 | 1.69 | |
| LogProbit | 0.889 | 244.74 | 0.413 | 0.0465 | |
| Weibull[e]<br>Quantal-Linear[f] | 0.374 | 244.66 | 1.48 | 0.973 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -0.67, 0.13, 0.93, -0.4, respectively.
[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[c] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[d] The Multistage 2° model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Quantal-Linear model.
[e] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[f] The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model.

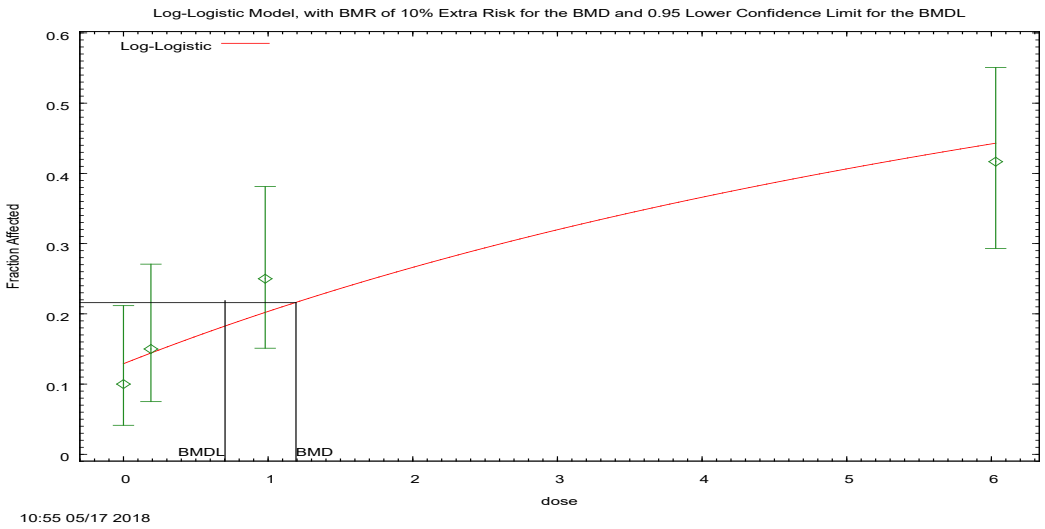


**Figure 24. Plot of incidence rate by dose with fitted curve for LogLogistic model for olfactory epithelial degeneration in the nasal cavity of male rats; dose shown in mg/m$^3$.**
**Logistic Model.** (Version: 2.15; Date: 3/20/2017)

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 = 1.19258

BMDL at the 95% confidence level = 0.702446

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.128811 | 0.1 |
| intercept | -2.3733E+00 | -2.1054E+00 |
| slope | 1 | 1 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -119.36 | 4 | | | |
| Fitted model | -120.1 | 2 | 1.47585 | 2 | 0.48 |
| Reduced model | -129.18 | 1 | 19.6499 | 3 | 0 |

AIC: = 244.194

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.1288 | 7.729 | 6 | 60 | -0.67 |
| 0.19 | 0.144 | 8.638 | 9 | 60 | 0.13 |
| 0.98 | 0.2017 | 12.102 | 15 | 60 | 0.93 |
| 6.03 | 0.4422 | 26.532 | 25 | 60 | -0.4 |

Chi^2 = 1.49 d.f = 2 P-value = 0.4749

## *4.17 BMDS Summary of olfactory epithelial degeneration in the nasal cavity of female rats*

**Table 41. Summary of BMD Modeling Results for Olfactory Epithelial Degeneration in the Nasal Cavity of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | ***p*-value** | **AIC** | | | |
| Gamma | 0.0521 | 256.02 | 5.23 | 1.68 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 3 model was selected based on the lowest AIC. |
| Dichotomous-Hill | N/A[b] | 258.02 | 5.42 | 0.988 | |
| Logistic | 0.133 | 254.23 | 3.50 | 2.26 | |
| LogLogistic | 0.0521 | 256.02 | 5.51 | 1.47 | |
| Probit | 0.133 | 254.24 | 3.44 | 2.18 | |
| LogProbit | 0.0579 | 256.09 | 0.291 | error[c] | |
| Weibull | 0.0521 | 256.02 | 5.53 | 1.68 | |
| **Multistage 3°** | **0.151** | **254.03** | **4.83** | **1.68** | |
| Multistage 2° | 0.146 | 254.09 | 4.33 | 1.67 | |
| Quantal-Linear | 0.128 | 254.32 | 3.08 | 1.63 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -1.1, 1.54, -0.45, 0, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.

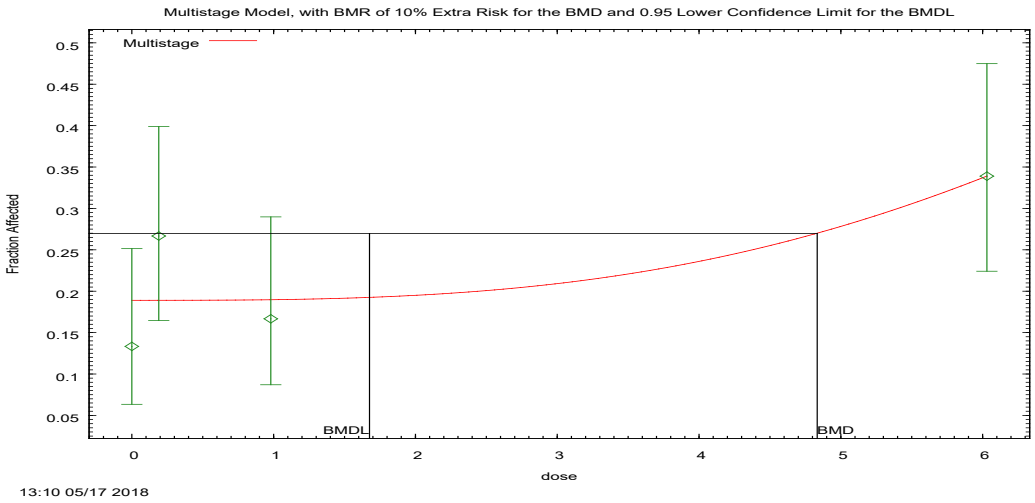


**Figure 25. Plot of incidence rate by dose with fitted curve for Multistage 3° model for olfactory epithelial degeneration in the nasal cavity of female rats; dose shown in mg/m$^3$. Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 4.83339

BMDL at the 95% confidence level = 1.67594

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0.188709 | 0.19072 |
| Beta(1) | 0 | 0 |
| Beta(2) | 0 | 0 |
| Beta(3) | 0.000933087 | 0.00092239 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -123.17 | 4 | | | |
| Fitted model | -125.02 | 2 | 3.69293 | 2 | 0.16 |
| Reduced model | -127.7 | 1 | 9.06722 | 3 | 0.03 |

AIC: = 254.033

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.1887 | 11.323 | 8 | 60 | -1.1 |
| 0.19 | 0.1887 | 11.323 | 16 | 60 | 1.54 |
| 0.98 | 0.1894 | 11.365 | 10 | 60 | -0.45 |
| 6.03 | 0.3388 | 19.99 | 20 | 59 | 0 |

Chi^2 = 3.79 d.f = 2 P-value = 0.1507

## *4.18 BMDS Summary of olfactory epithelial hyperplasia in the nasal cavity of combined rats*

**Table 42. Summary of BMD Modeling Results for Olfactory Epithelial Hyperplasia in the Nasal Cavity of Combined Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma[b]<br>Weibull[c]<br>Multistage 3°[d]<br>Multistage 2°<br>Quantal-Linear | 0.210 | 497.10 | 2.05 | 1.41 | Of the models that provided an adequate fit and a valid BMDL estimate, the LogLogistic model was selected based on the lowest AIC. |
| Dichotomous-Hill | 0.100 | 498.56 | 1.01 | 0.231 | |
| Logistic | 0.176 | 497.53 | 2.73 | 2.15 | |
| **LogLogistic** | **0.223** | **496.95** | **1.82** | **1.17** | |
| Probit | 0.180 | 497.48 | 2.64 | 2.05 | |
| LogProbit | 0.191 | 497.64 | 0.433 | 0.0324 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were -1.21, 1.23, 0.11, -0.13, respectively.
[b] For the Gamma and Weibull models, the power parameter estimates were 1 (boundary of parameter space). For the Gamma model, the power parameter estimate was 1. The model is equivalent to the Quantal-Linear model.
[c] For the Weibull and Gamma models, the power parameter estimates were 1 (boundary of parameter space). For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.

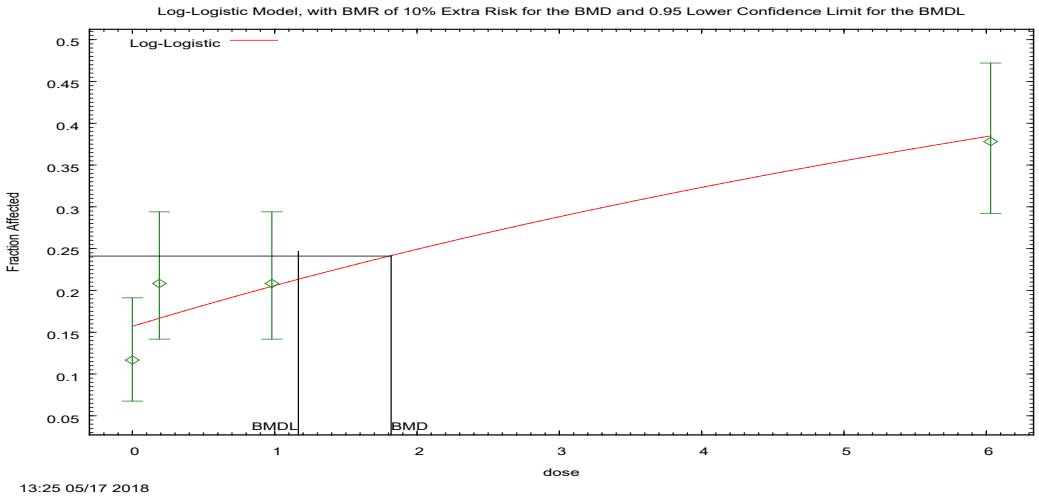


**Figure 26. Plot of incidence rate by dose with fitted curve for LogLogistic model for olfactory epithelial hyperplasia in the nasal cavity of combined rats; dose shown in mg/m$^3$.**
**Logistic Model.** (Version: 2.15; Date: 3/20/2017)

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 = 1.81806

BMDL at the 95% confidence level = 1.16662

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| background | 0.156784 | 0.116667 |
| intercept | -2.7950E+00 | -2.4260E+00 |
| slope | 1 | 1 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -244.96 | 4 | | | |
| Fitted model | -246.48 | 2 | 3.03201 | 2 | 0.22 |
| Reduced model | -256.89 | 1 | 23.8624 | 3 | <.0001 |

AIC: = 496.953

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.1568 | 18.814 | 14 | 120 | -1.21 |
| 0.19 | 0.1665 | 19.976 | 25 | 120 | 1.23 |
| 0.98 | 0.2044 | 24.532 | 25 | 120 | 0.11 |
| 6.03 | 0.3839 | 45.678 | 45 | 119 | -0.13 |

Chi^2 = 3 d.f = 2 P-value = 0.2226

## *4.19 BMDS Summary of bronchiolo-alveolar hyperplasia in the lungs of female rats*

**Table 43. Summary of BMD Modeling Results for Bronchiolo-Alveolar Hyperplasia in the Lungs of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.777 | 198.41 | 0.775 | 0.320 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 3° model was selected based on the lowest AIC/BMDL. |
| Dichotomous-Hill LogLogistic | 0.777 | 198.41 | 0.864 | 0.502 | |
| Logistic | 0.680 | 197.17 | 0.387 | 0.298 | |
| Probit | 0.700 | 197.06 | 0.383 | 0.286 | |
| LogProbit | 0.777 | 198.41 | 0.787 | 0.474 | |
| Weibull | 0.777 | 198.41 | 0.783 | 0.288 | |
| **Multistage 3°** | **0.952** | **196.43** | **0.660** | **0.216** | |
| Multistage 2° | 0.909 | 196.52 | 0.539 | 0.237 | |
| Quantal-Linear | 0.0581 | 203.90 | 0.194 | 0.147 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.22, -0.22, 0, 0, respectively.

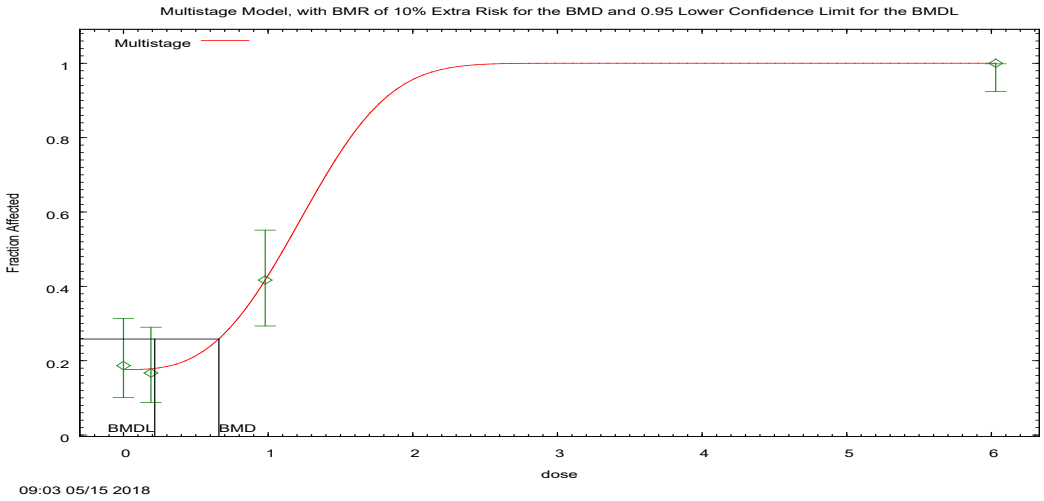


**Figure 27. Plot of incidence rate by dose with fitted curve for Multistage 3° model for bronchiolo-alveolar hyperplasia in the lungs of female rats; dose shown in mg/m³. Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 0.659531

BMDL at the 95% confidence level = 0.216284

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0.175529 | 0 |
| Beta(1) | 0 | 0 |
| Beta(2) | 0 | 0 |
| Beta(3) | 0.367259 | 4.5674E+17 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -96.17 | 4 | | | |
| Fitted model | -96.21 | 2 | 0.0977349 | 2 | 0.95 |
| Reduced model | -163.32 | 1 | 134.305 | 3 | <.0001 |

AIC: = 196.429

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.1755 | 10.356 | 11 | 59 | 0.22 |
| 0.19 | 0.1776 | 10.656 | 10 | 60 | -0.22 |
| 0.98 | 0.4165 | 24.989 | 25 | 60 | 0 |
| 6.03 | 1 | 59 | 59 | 59 | 0 |

Chi^2 = 0.1 d.f = 2 P-value = 0.9523

## *4.20 BMDS Summary of interstitial fibrosis in the lungs of female rats*

**Table 44. Summary of BMD Modeling Results for Interstitial Fibrosis in the Lungs of Female Rats**

| Model[a] | Goodness of fit | | $BMD_{10Pct}$ ($mg/m^3$) | $BMDL_{10Pct}$ ($mg/m^3$) | Basis for model selection |
|---|---|---|---|---|---|
| | *p*-value | AIC | | | |
| Gamma | 0.986 | 115.93 | 0.749 | 0.379 | Of the models that provided an adequate fit and a valid BMDL estimate, the Multistage 3° model was selected based on the lowest AIC/BMDL. |
| Dichotomous-Hill LogLogistic | 0.986 | 115.93 | 0.866 | 0.531 | |
| Logistic | 0.852 | 114.24 | 0.574 | 0.471 | |
| Probit | 0.797 | 114.38 | 0.532 | 0.432 | |
| LogProbit | 0.983 | 115.93 | 0.753 | 0.505 | |
| Weibull | 0.981 | 115.93 | 0.749 | 0.352 | |
| **Multistage 3°** | **0.996** | **113.93** | **0.658** | **0.314** | |
| Multistage 2° | 0.925 | 114.09 | 0.539 | 0.321 | |
| Quantal-Linear | 0.0127 | 126.65 | 0.215 | 0.170 | |

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.19, 0.98, and 6.03 $mg/m^3$ were 0.06, -0.06, 0, 0, respectively.

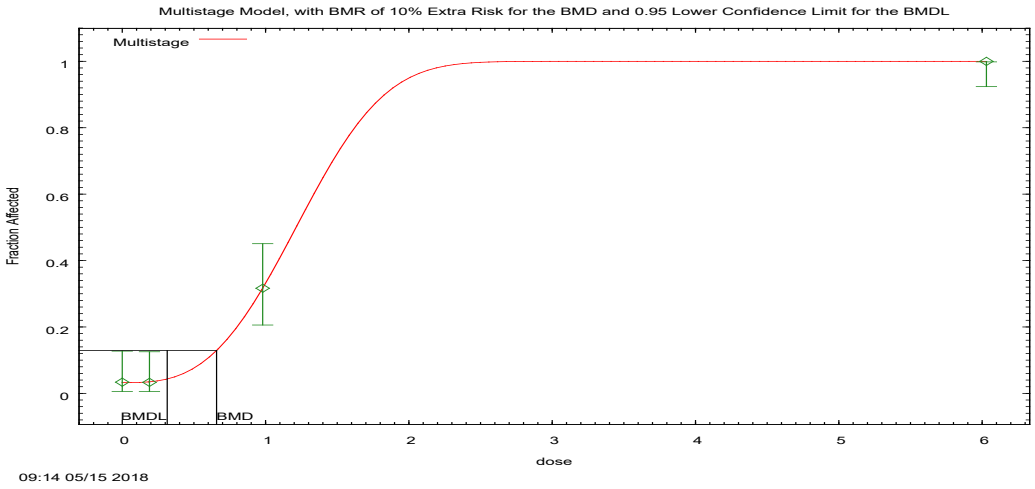


**Figure 28. Plot of incidence rate by dose with fitted curve for Multistage 3° model for interstitial fibrosis in the lungs of female rats; dose shown in mg/m$^3$.**
**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

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 = 0.658183

BMDL at the 95% confidence level = 0.313838

**Parameter Estimates**

| Variable | Estimate | Default Initial Parameter Values |
|---|---|---|
| Background | 0.0324338 | 0 |
| Beta(1) | 0 | 0 |
| Beta(2) | 0 | 0 |
| Beta(3) | 0.369521 | 4.5674E+17 |

**Analysis of Deviance Table**

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---|---|---|---|---|---|
| Full model | -54.96 | 4 | | | |
| Fitted model | -54.97 | 2 | 0.00831754 | 2 | 1 |
| Reduced model | -153.27 | 1 | 196.618 | 3 | <.0001 |

AIC: = 113.934

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid. |
|---|---|---|---|---|---|
| 0 | 0.0324 | 1.914 | 2 | 59 | 0.06 |
| 0.19 | 0.0349 | 2.093 | 2 | 60 | -0.06 |
| 0.98 | 0.3167 | 19 | 19 | 60 | 0 |
| 6.03 | 1 | 59 | 59 | 59 | 0 |

Chi^2 = 0.01 d.f = 2 P-value = 0.9959