Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the July 2019 Proposed Methylene Diphenyl Diisocyanate (MDI) and 1,6—Hexamethylene Diisocyanate (HDI) and all isomers Development Support Document

The Development Support Document (DSD) for Methylene Diphenyl Diisocyanate (MDI) and 1,6—Hexamethylene Diisocyanate (HDI) and all isomers was proposed in March 2019. The American Chemistry Council Diisocyanates Panel and Aliphatic Diisocyanates Panel ("hereafter collectively refer to as, "ACC") submitted comments on the proposed DSD. The TCEQ appreciates the effort put forth to provide comments on this proposed DSD for MDI and HDI. The goal of the Toxicology, Risk Assessment, and Research Division and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. The TCEQ thanks ACC for participating in this process in the form of providing scientific references and for taking the time to provide comments on this proposed DSD for MDI and HDI. Substantive comments were divided into sections and are provided below, followed by TCEQ responses.

ACC Comments

Substantive comments relevant to the derivation of toxicity factors are provided and addressed by the TCEQ below.

Comment 1:

Identification of Health-Based Acute (1-hour) ReV - Aerosol

In its draft Development Support Document (DSD) for 4,4-methylene diphenyl diisocyanate (MDI) and 1,6-hexamethylene diisocyanate (HDI), the TCEQ (2019) reviewed available inhalation studies on aerosols of both substances and identified two key studies (Pauluhn et al., 1999 for MDI; Lee et al., 2003 for HDI) suitable for Point of Departure (POD) selection and Acute (1-h) Reference Value (ReV) derivation. TCEQ subsequently decided Pauluhn et al. (1999) was the better of the two studies for these purposes. ACC agrees with the selection of 2.4 mg/m3 as a candidate point of departure (POD) but believes Pauluhn at al. (1999) may not provide the best support for this value without a rationale from TCEQ as to why an adaptive change in tidal volume represents an adverse effect or is an immediate precursor to same (TCEQ, 2015).

TCEQ Response:

The TCEQ considers sensory irritation as an adverse effect. In the present case, tidal volume changes are in response to (i.e., indicators of) the underlying adverse irritation. Toxicity factors are generally based on mild/sensitive adverse effects such as mild irritation.

Comment 2:

pMDI POD - Pauluhn et al. (1999)

Groups of male Wistar rats (n = 6) were exposed to conditioned air for 30 min followed by a 150 min exposure to pMDI aerosol at one of five concentrations (0, 2.4, 6.7, 15.8, or 38.7 mg/m^3). During this time, respiratory parameters (respiratory rate and tidal volume) were averaged over 1-min intervals. Data were normalized to the mean of the 30-min pre-exposure period which was assigned a value of 100%. Pauluhn et al. (1999) reported that respiratory rates at 2.4 and 6.7 mg/m^3 were indistinguishable from the air control group, while rates in the two highest exposure groups were ~20% higher than pre-exposure control. In contrast, concentration-dependent effects on tidal volume were observed; Figure 2 from Pauluhn et al. (1999) depicting these data is reproduced below for ease of reference.

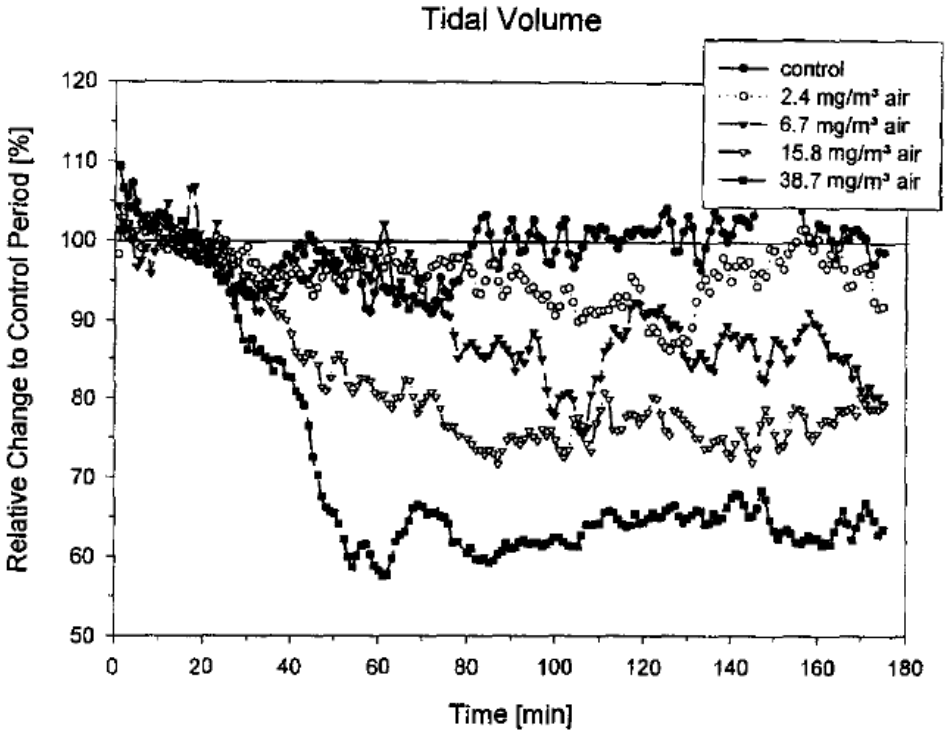

FIGURE 2. Analysis of concentration dependence of tidal volume. After acclimatization, the rats (n = 6) were exposed for 30 min to air (collection of baseline data). Subsequently the rats were exposed to PMDI for 150 min.

- First, the data in Figure 2 above clearly show that during the first 60 min of exposure to pMDI, the time frame targeted by an Acute (1-h) ReV, the tidal volume measured at 2.4 mg/m^3 is indistinguishable from control. While tidal volumes at 2.4 mg/m^3 after 60 min are observed to decrease randomly to values 0 – 15% below the corresponding control values, this result is precisely what would be predicted for a reactive aerosol that gradually begins to overwhelm natural defense mechanisms in the airways, eventually leading to a subtle, non-adverse decrease in tidal volume.

- Second, TCEQ provides no rationale for its position that this minimal adaptive / reflexive change in tidal volume after 1-h of exposure is either adverse or an "immediate precursor" (TCEQ, 2015) to an adverse effect. Indeed, as discussed in our earlier comments (ACC, 2018a), adverse effects (i.e., cytotoxicity) at 2.4 mg/m^3 are not seen

even after an exposure duration of 6 h (Pauluhn, 2000), although they can occur at higher concentrations (3.3 – 7.2 mg/m^3) when daily 6-h exposures are extended over a two-week to 13-week period (Reuzel et al., 1994a; Pauluhn et al., 1999; Kilgour et al., 2002).

TCEQ Response:

In regard to the first bullet, exposure to 2.4 mg PMDI/m^3 caused minimal acute pulmonary irritation as indicated by up to ≈14% decrease in tidal volume at the 120-130 min time point, which is at 90-100 min (1.5 h) of chemical exposure. Accordingly, a 1.5-h minimal lowest-observed-adverse-effect-level (LOAEL) of 2.4 mg/m^3 was identified from this acute exposure study. The TCEQ considers effects due to 1.5 h of exposure as relevant to the derivation of a 1-h ReV/ESL. The TCEQ further notes that 6.7 mg/m^3 could be used as a 1-h LOAEL based on a >20% decrease in tidal volume at around 1-h of exposure, and that in conjunction with a standard LOAEL-to-NOAEL uncertainty factor (UF_L) of 3, would result in an 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. Lastly, the TCEQ disagrees that these decreases in tidal volume are not indicative of an underlying adverse effect, namely irritation (see TCEQ response to ACC comment 1).

In regard to the second bullet, 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. This rationale and information have been added to the DSD.

Comment 3:

As summarized in our earlier comments (ACC, 2018a), these studies exhibited relatively consistent NOAELs that ranged from 2.4 mg/m^3 for one 6-h exposure to ≥ 1.4 mg/m^3 for 65 daily 6-h exposures and provide a rich dataset from which to select a POD. However, in the process of identifying a suitable POD, TCEQ ignores results from longer exposure duration studies despite its guidance (TCEQ, 2015) that states “It is acceptable risk assessment practice to incorporate longer-term data from toxicity studies to develop acute toxicity values corresponding to shorter duration exposures when it is justified by the MOA analysis”. As outlined by TCEQ (2019) and detailed by Pauluhn (2011), MDI-induced pulmonary toxicity is initiated at points of pMDI deposition in the respiratory tract where it readily reacts with macromolecular nucleophiles (e.g., glutathione, peptides, tissue proteins). As the local nucleophilic capacity is overwhelmed and surfactant becomes increasingly dysfunctional, cytotoxicity and inflammation can ensue. On an acute scale, these effects can be seen as increases in lung weight as well as BALF levels of intracellular enzymes (LDH, γ-GT), plasma protein (ACE) and inflammatory cells. On a chronic scale, when the acute effects become biologically significant, they are manifested as olfactory epithelial cell degeneration in the nasal cavity and pulmonary fibrosis. Thus, the pMDI concentrations in subchronic studies that do not

induce histopathological lesions in the respiratory tract provide critical information that can help differentiate homeostatic changes from adverse effects. Because histopathological examinations are typically conducted only in subchronic studies, the 13-wk studies by Reuzel et al. (1994a) with pMDI should be considered among the studies used to derive an acute ReV. The NOAEL of 1.4 mg/m^3 reported by Reuzel et al. (1994a) based on the absence of histological changes in the respiratory tract and lung weight changes is conservative. As stated by the authors "… the "no-observed-adverse-effect level" of polymeric MDI was 1.4 mg/m^3, the actual no-adverse-effect level being lower than but most probably very close to 4.1 mg/m^3." The weight of evidence from multiple acute to subchronic studies with pMDI do not support a 1-h LOAEL of 2.4 mg/m^3.

TCEQ Response:

It is not true that "in the process of identifying a suitable POD, TCEQ ignores results from longer exposure duration studies despite its guidance (TCEQ, 2015)." Section 3.1.3 of the DSD, *Selection of the Key Study, POD and Critical Effect*, considers and discusses numerous studies of up to 4 wks in duration. For example, Table 8 below is a summary table that appears in that section. While the commenter petitions the TCEQ to use respiratory tract histopathological lesions and lung weight changes as the critical endpoint(s) based on a 13-wk rat study (NOAEL of 1.4 mg/m^3 as reported by Reuzel et al. 1994a), use of the minimal LOAEL identified by the TCEQ is slightly more conservative (minimal LOAEL of 2.4 /UF_L of 2 = 1.2 mg/m^3 as a NOAEL) and based on a milder type of adverse effect (irritation) from an acute rat study, which is all together more appropriate for deriving an acute ReV/ESL. Regardless, it is noted that the NOAEL-based PODs of 1.4 mg/m^3 (proposed by ACC) and 1.2 mg/m^3 (selected by TCEQ) are remarkable similar.

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 (Wevel 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)

Comment 4:

POD_{HEC} and RDDR Calculations – Pauluhn et al. (1999)

The human equivalent POD concentration (POD_{HEC}) was derived by multiplying the TCEQ-identified POD for pMDI aerosol in rats (2.4 mg/m^3) by the Regional Deposited Dose Ratio (RDDR). As shown below, the RDDR is calculated using human and animal inputs for minute ventilation (VE), deposition fraction (DF) and normalizing factor (NF) for the region(s) of interest, where NF is commonly based on the surface area of the lung region(s) of interest. The TCEQ used the Multi-Path Particle Dosimetry (MPPD) model to derive the human and animal DF values. ACC has three concerns with the TCEQ RDDR calculation.

First, TCEQ provides no rationale for its human minute volume (VE_H) of 13,800 ml/min. Apparently, this value comes from USEPA (1994) where it is listed as the default VE_H used in an earlier version (Version 2.2) of the MPPD software. However, the MPPD software has been repeatedly revised over the past 25 years and version 2.2 is no longer available. Default inputs for the human deposition model (Yeh and Schum) used in the most current version (v3.04) of the MPPD model are a breathing frequency of 12/min and a tidal volume of 625 ml; these values result in a VE_H of 7,500 ml/min, not 13,800 ml/min. However, a VE_H of 7,500 ml/min approximates that of a resting individual and may underestimate the VE_H of the human receptor population the acute ReV is designed to protect. ACC believes the VE_H for a 24-h day should be based on a respiratory rate approaching that associated with light activity, which would reflect a balance between time spent sleeping and performing heavy activities. Using long-term human inhalation rates recommended by USEPA (2011; Table 6-1) for 13 age groups between birth and 81 years of age, the latter value corresponding to the average lifespan[3] for the receptor population of interest, a mean age-weighted inhalation rate of 14.51 m^3/day can be derived. This value corresponds to a VE_H of 10,080 ml/min and a tidal volume of 630 ml (10,080 ml/min ÷ 16 breaths/min). The breathing frequency of 16/min falls halfway between human breathing frequencies (USEPA, 2004) associated with rest (12/min) and light exercise (20/min) and is comparable to that used by TCEQ (16.43/min). When these receptor-specific values are used in the MPPD human model, the resulting human Deposition Fraction (DF_H) is 0.1675 (Figure 1). ACC believes the VE_H of 10,080 ml/min is not only health protective, falling just below a VE_H of 12,160 ml/min[4] for individuals spending the whole day performing light activities, but it also provides a stronger scientific basis for derivation of regulatory air concentration limits than an unsupported default value.

TCEQ Response:

The human minute volume used by the TCEQ was originally derived for use in the USEPA RDDR calculation prior to development of the MPPD model. When the MPPD model was developed, the TCEQ adjusted the default tidal volume and breathing frequency that the model used to match the minute volume used in the other RDDR model to keep consistency across calculations. As mentioned by ACC, a minute volume of ~12,000 ml/min is associated with performing light activities, and using the model defaults to calculate a minute volume of 7,500 ml/min would not be protective. Therefore, in order to be conservative in the absence of specific information, use of the well established human minute volume of 13,800 ml/min was used. Additionally, the USEPA 2012 “Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment” still recommends/supports using the default human minute volume of 13,800 ml/min, so this value was not changed.

Comment 5:

Second, although TCEQ provides a reasonable rationale for use of MPPD’s Long-Evans (L-E) Asymmetric deposition model, its implementation of the model is incomplete. The L-E model is based on a 330 g rat, while the mean body weight of the Wistar rats used by Pauluhn et al. (1999) is 31% lower (228 g). Although TCEQ appropriately lowered the L-E model’s default tidal volume (2.06 ml) to correspond to that of the smaller Wistar rats (1.634 ml[5]), it did not similarly

adjust other default respiratory parameters such as Functional Residual Capacity (FRC, 4.0 ml) and Head volume (0.42 ml). Using the scaling function incorporated into the MPPD Sprague-Dawley model[6], the FRC and Head volume for a 228 g Wistar rat were determined to be 2.99859 ml and 0.34313 ml, respectively[7]. When the L-E Asymmetric model is run with the smaller FRC and Head volumes, the rat Deposition Fraction (DF_A) for the tracheobronchial and pulmonary regions is 0.0829 (Figure 2).

TCEQ Response:

Default values are commonly used in risk assessment in the absence of experiment- or species-specific data to account for uncertainty and to provide consistency across assessments. The tidal volume in the MPPD model was changed because it did not accurately compute with the calculated minute volume and the model's tidal volume (minute volume = tidal volume x breathing frequency; 36.8342 mL/min = 0.23 mL x 160 breaths/min). There was no other specific information available to adjust any of the other parameters for the study used or in the Long-Evans model, so the other breathing parameters were not adjusted.

Comment 6:

Third, the human and rat NF values for the combined tracheobronchial and pulmonary regions are inappropriate. The NF_H value of 543,200 cm^2 is the default value provided by USEPA (1994) based on publications by Mercer et al. (1994a, 1994b). However, USEPA (2004) currently recommends a value of 576,420 cm^2 based on human morphology given by Yeh and Schum (1980), *developers of the human deposition model incorporated into the MPPD software*. TCEQ also used the default NF_A value (3422.5 cm_2) listed by USEPA (1994) for the surface areas of the tracheobronchial and pulmonary regions of rats without any adjustment for the small size of rat used in the Pauluhn study. The NF_A for a 228 g rat is 3,204.1 cm^2 based on equation [56.982*(BW)^0.74213] published by the MPPD model developers (Miller et al., 2014)[5]. When these DF values are combined with human- and rat-specific variables discussed above, the resultant RDDR is 1.4724. Using the revised RDDR and a POD_{ADJ} of 2.4 mg/m^3, the human equivalent POD concentration (POD_{HEC}) is 3.5338 mg/m^3 (Table 1).

TCEQ Response:

The TCEQ was unable to locate the cited USEPA 2004 document as the USEPA website states that this article has been archived. However, based on the latest guidance, USEPA 2012 "Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment" Table 2-3 still recommends using the default surface areas used by TCEQ, so these values were not changed.

Comment 7:

pHDI POD - Lee et al. (2003)

Groups of male C57BL/6J mice (n = 4-6) were exposed to pHDI aerosol dissolved in acetone for 5-h at one of three concentrations (0, 1.30, 10.83 mg/m^3) and examined for multiple endpoints at 0, 6, 18, 42, 90, 186 and 378 h post-exposure as summarized by TCEQ (2019). Consistent with

the Pauluhn et al. (1999) data in rats, signs of pulmonary irritation (increased Penh) were seen immediately after exposure, returning to control levels at 6-h (1.30 mg/m^3) and 42-h (10.83 mg/m^3) post-exposure. Transient, concentration-dependent changes that resolved by study end included: increases in lung weight, lavage fluid protein, lavage fluid neutrophils and macrophages, as well as hypertrophy and hyperplasia in the terminal bronchioles and alveolar ducts. However, in the absence of data on cytotoxicity (e.g., lactate dehydrogenase), it cannot be ascertained whether these effects are adverse or simply reflect adaptive responses to the transient presence of dysfunctional surfactant caused by the deposition of diisocyanate. Such homeostatic / adaptive responses would include (a) the release of protein by lung parenchymal cells (e.g., Type II cells) associated with the replacement of dysfunctional surfactant, (b) the influx of plasma protein / fluid due to a transient increase in the permeability of the alveolar-endothelial barrier caused by the increased surface tension due to the depletion of surfactant, and (c) increased cellular activity associated with these adaptive changes. Although the TCEQ (2015) recognizes that a statistically significant effect is not synonymous with an adverse effect, it determined, without accompanying rationale, that the effects noted by Lee et al. (2003) were adverse and identified the low pHDI concentration (1.30 mg/m^3) as the LOAEL.

Further support for the ACC position that effects reported by Lee et al. (2003) at 1.30 mg/m^3 were adaptive, not adverse, can be found in the studies performed by Pauluhn and Mohr (2001). In these studies, rats were exposed to pHDI 6h/day, 5 d/wk for either 2 weeks (1.2, 4.6, 16.3 or 69.2 mg/m^3) or 3 weeks (4.3, 14.7 or 89.8 mg/m^3). As summarized by TCEQ (2019, pg 18), wet lung weights, cell and protein content of bronchoalveolar lavage fluid, multiple lung function measurements, cytotoxicity (e.g., LDH, γ-GT), proliferative responses in the nasal and bronchiolo-alveolar regions, inflammation, and fibrosis were not seen at pHDI concentrations ≤ 4.6 mg/m^3. In addition, as described below, rats are more sensitive to the effects of pHDI than mice (Pauluhn, 2008).

TCEQ Response:

The commenter acknowledges that consistent with data in rats (Pauluhn et al. 1999), signs of pulmonary irritation were seen in mice immediately after 5-h exposure to 1.3 or 10.83 mg/m^3. As alluded to above (TCEQ Response to Comment 1), the TCEQ considers an indication of irritation itself as an adverse effect (e.g., no histopathology or additional adverse effects are required to co-occur). Thus, this acknowledgment is supportive of TCEQ using 1.3 mg/m^3 as a mouse LOAEL. Toxicity factors should be based on mild, reversible adverse effects such as irritation. Consistent with this guiding principle for the protection of public health, there was a return to control levels at 6-h (1.30 mg/m^3) and 42-h (10.83 mg/m^3) post-exposure, as well as for some other concentration-dependent changes noted by the commenter (e.g., lung weight). The TCEQ's rationale for the LOAEL was clearly stated in the DSD… "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", and the commenter did not specifically refute the adversity of these effects other than stating that their adversity cannot be ascertained in the absence of data on cytotoxicity. However, the TCEQ disagrees that a demonstration of cytotoxicity or histopathological changes is required for a finding of adversity for effects that TCEQ deems adverse themselves (e.g., irritation, functional impairment, organ weight changes,

etc.). In regard to the Pauluhn and Mohr (2001) study cited by the commenter, negative findings in one rat study do not necessarily negate positive findings in a different mouse study. Regardless, the acute POD ultimately selected by the TCEQ (minimal 1.5-h LOAEL of 2.4 mg/m^3 for mild irritation/decreased tidal volume in Pauluhn et al. 1999) would not change (see Section 3.1.3.3 of the DSD).

Comment 8:

POD_{HEC} and RDDR Calculations - Lee et al. (2003)

ACC was unable to replicate the MPPD outputs for humans (Figure 7) and mice (Figure 8; strain modeled by TCEQ not provided) reported by TCEQ (2019) using the current version (3.04) of the MPPD software. In the absence of body weight (BW) data from Lee et al. (2003), TCEQ used the default BW for male B6C3F1 mice of 0.0316 kg (USEPA, 1994). Using this BW and USEPA (1994) methodology, ACC determined a mouse ventilation rate of 36.3842 ml/min (not 32.9019 ml/min as calculated by TCEQ). Using the breathing frequency of 160 breathes/min selected by TCEQ (i.e., comparable to the value of 163 breathes/min for mice; Inglis, 1980), the tidal volume was determined to be 0.2274 ml (not 0.20 ml). The aerosol characteristics were those from Lee et al. (2003), except that the density of the aerosol was 1.14 g/ml (Covestro, 2019), not the 1.04 g/ml used by TCEQ. Using these data along with the aerosol characteristics from Lee et al. (2003) as inputs to the most current version (3.04) of the MPPD software, the human and rat deposition fractions in the targeted tracheobronchial and pulmonary regions were 0.1203 (not 0.1222) and 0.0971 (not 0.0439), respectively (Figures 3 and 4). After changing the mouse normalizing factor (NF) from 506.5 to 503.5 to exclude contribution of the extrathoracic (ET) region, the RDDR was calculated to be 3.3354. The TCEQ-identified PODADJ of 2.223 mg/m^3 and a revised RDDR of 3.3354 results in a PODHEC of 7.4146 mg/m^3. TCEQ Response:

TCEQ Response:

The TCEQ acknowledges and has corrected the errors in the model. The TCEQ also agrees with the suggested changes from ACC and have responded with the following changes: mouse minute volume (36.8342 mL/min), mouse breathing frequency (160 breaths/min), tidal volume (0.23 mL), surface area (503.5 cm^2) and density (1.14 g/cm^3). Human minute volume and surface area were kept as is due to reasons described above.

Comment 9:

Selection of Key Study – Pauluhn et al. (1999) vs. Lee et al. (2003)

The Acute ReV is targeted to be a concentration that is free of adverse effects when inhaled for a period of approximately 1 hour. The POD for this endpoint is best supported by results from the Pauluhn et al (1999) study. Using a series of ~60-paired measurements of tidal volume over the initial 60-min exposure period, the author demonstrated that the tidal volumes measured at a pMDI concentration of 2.4 mg/m^3 were superimposable over that measured in control air. While a transient / minimal decrement in tidal volume is not itself adverse (see §3.6.1.4.1; TCEQ, 2015), the more significant decrements in tidal volume that occur at higher pMDI concentrations and/or longer exposure durations when pulmonary defense buffers (e.g.,

glutathione, surfactant) are depleted could be seen as a precursor to an adverse lung effect (e.g., cytotoxicity). As discussed by ACC (2018a), this prediction is consistent with results of an acute (6-h) pMDI aerosol inhalation study in rats (Pauluhn, 2000) that showed adaptive effects to lung irritation at pMDI concentrations of 0.7 mg/m3 and 2.4 mg/m^3 (NOAEL) and adverse effects (e.g., cytotoxicity) at ≥ 8 mg/m^3 (LOAEL).

Scientifically, an Acute ReV is less well supported by the Lee et al. (2003) results. First, endpoints evaluated in this study were measured at 5 hours, a time frame well outside the targeted exposure duration of 1 hour for an Acute ReV. While changes were seen at this time, it is uncertain if the effects were adverse (TCEQ position) or simply a reflection of the transient, adaptive processes associated with irritation since the study did not include any enzymatic (e.g., LDH) or histological evidence of cytotoxicity. Second, endpoint uncertainty is compounded by the fact that the current MPPD model does not include an asymmetric mouse lung model. The Deposition Fraction (DFA) derived by ACC from the symmetric B6C3F1 mouse lung model (the B6C3F1 strain was used by TCEQ for mouse BW) may over- / under-estimate the DFA for the asymmetric lung geometry of the C57BL/6J mice used by Lee et al. (2003). Finally, as described below, at polyisocyanate concentrations relevant to derivation of an Acute ReV (i.e., ≤ 10 mg/m^3), rats are more sensitive to pMDI than pHDI.

TCEQ Response:

The TCEQ agrees that a POD for the acute ReV is best supported by results from the Pauluhn et al (1999) study as opposed to the Lee et al. (2003) study. The acute ReV POD continues to be based on the Pauluhn et al. (1999) study. The commenter's concerns about the adversity of endpoints in Lee et al. (2003) and the MPPD mouse lung model should be somewhat mitigated by the fact that the TCEQ continues to use an acute ReV POD based on results from the Pauluhn et al (1999) study.

Comment 10:

Pauluhn (2008) exposed Wistar rats and C57BL6J mice for a period of 6-h to respirable aerosols of pHDI (free NCO content of 22.8%) at a concentration of 10 mg/m^3. As shown in Table 2 from this publication, bronchoalveolar lavage data collected 20-h post-exposure showed rats were more sensitive than mice to the effects (e.g., increases in lung weight, cytotoxicity, inflammation) induced by pHDI exposure. Under these same exposure conditions (Pauluhn, 2002), bronchoalveolar lavage data collected from Wistar rats exposed to aerosols of either pMDI (31% free NCO) or pHDI (22% free NCO) exhibited comparable adverse effects (i.e., BALF increases in total protein and ACE), although pMDI was more potent than pHDI at concentrations ≤ 10 mg/m^3 (see Figure 7). Data from these studies demonstrate that (a) rats are more sensitive than mice to effects induced by inhalation of pHDI, and (b) the effects seen in rats with pMDI occur at lower concentrations than those seen with pHDI. Thus, adverse effects observed in rats with pMDI provide a conservative (health protective) basis for derivation of an acute ReV. This conclusion is consistent with the acute PODHEC value derived for pMDI in rats (3.5338 mg/m^3) being lower than that derived for pHDI in mice (7.4146 mg/m^3).

TCEQ Response:

Consistent with comments on the sensitivity of rats and that effects seen in rats with pMDI occur at lower concentrations than those seen with pHDI, the acute ReV is based on an acute study in rats exposed to pMDI (Pauluhn et al. 1999). In this case, the TCEQ agrees that adverse effects observed in rats with pMDI provide a conservative (health protective) basis for derivation of an acute ReV, particularly given that the TCEQ's PODHEC (1.6293 mg/m^3) is more conservative than that cited or proposed by the commenter.

Comment 11:

Acute (1-h) ReV Derivation – Pauluhn et al. (1999)

Table 1 presents acute ReV and ESL values for pMDI aerosol derived using variables selected by either TCEQ (black text) or ACC (red text). In addition to the alternative RDDR calculated by ACC (see above), the rationale for Uncertainty Factors (UF) chosen by ACC is provided below. The Acute (1-h) ReV (rounded to two significant digits) derived by ACC is 390 µg/m^3; the Acute (1-h) ReV proposed by TCEQ (2019) is 27 µg/m^3.

TCEQ Response:

The acute ReV proposed by the commenter (390 µg/m^3) is significantly above even the OSHA short-term exposure level (STEL) ceiling (200 µg/m^3). Based on this and considering the scientific judgments in TCEQ's own derivation, the TCEQ considers the 390 µg/m^3 proposed by the commenter as inadequate for the protection of the general public's health. By corollary, as a whole, the proposed POD and UF values proposed in the comments below are also considered inadequate for the protection of the general public's health.

Comment 12:

LOAEL to NOAEL UF.

As discussed above, the change identified by TCEQ as adverse (i.e., minimal decrease in tidal volume) can best be described as an adaptive, non-adverse effect, particularly when compared to other relatively severe effects TCEQ considers non-adverse (§3.6.1.4.1; TCEQ, 2015). However, because the minimal decrease seen at 2.4 mg/m^3 occurs only after 1-h of exposure, this effect is best described as a NOEL for the exposure period targeted by the Acute (1-h) ReV, or at worse a NOAEL, if TCEQ can provide a rationale for its claim this change is adverse. Either way, no exposure duration adjustment would be required resulting in a PODADJ of 2.4 mg/m^3. The identification of 2.4 mg/m^3 as a NOAEL is also consistent with results of a subchronic study (Reuzel et al., 1994a) in rats, more sensitive than mice to the effects of pHDI (Pauluhn, 2008), that reported daily 6-h exposures to pMDI did not cause adverse effects in the respiratory tract at a 1.4 mg/m^3. Using an admittedly conservative methodology, TCEQ (2019, pg 34) adjusted the NOAEC for HDI vapor from a subacute exposure (5 h/d, 5 d/wk for 3 weeks) to a 1-h POD. This same approach can be applied to the pMDI NOAEC of 1.4 mg/m^3 to derive an ultra-conservative 1-h POD of 2.54 mg/m^3 [$((1.4\ mg/m^3)^3 \times 6\ h \div 1\ h)^{1/3}$]. Judged from either

perspective, there is no justification for the TCEQ application of a 2-fold UF for LOAEL to NOAEL extrapolation.

TCEQ Response:

The TCEQ considers sensory irritation as an adverse effect. In the present case, tidal volume changes are in response to (i.e., indicators of) the underlying adverse irritation. Toxicity factors should be based on mild/sensitive adverse effects such as mild irritation. Exposure to 2.4 mg PMDI/m^3 caused minimal acute pulmonary irritation as indicated by up to ≈14% decrease in tidal volume at the 120-130 min time point, which is at 90-100 min (1.5 h) of chemical exposure. Accordingly, a 1.5-h minimal LOAEL of 2.4 mg/m^3 was identified from this acute exposure study. The TCEQ considers effects due to 1.5 h of exposure as relevant to the derivation of a 1-h ReV/ESL and agrees that no duration adjustment is required. Without a NOAEL, a minimal UFL of 2 is required for a minimal LOAEL. The TCEQ further notes that 6.7 mg/m^3 could be used as a 1-h LOAEL based on a >20% decrease in tidal volume at around 1-h of exposure, and that in conjunction with a standard UF_L of 3, would result in an identical POD as use of the minimal LOAEL of 2.4 mg/m^3 with the minimal UF_L of 2.

Comment 13:

UFs for Interspecies (UFA) and Intraspecies (UFH) Variation

In deriving the acute ReV for pMDI, TCEQ (2019) relied on uncertainty factors of 3 to account for interspecies variation (UFA; considers toxicodynamic factors only since toxicokinetic differences were accounted for using the RDDR approach) and 10 to account for intraspecies variation (UFH). Due to the mode of action for MDI (i.e., irritation at the portal of entry due to reaction of macromolecules with the parent chemical), these default values are likely to be overly conservative. Consistent with TCEQ guidelines for deriving ReVs (TCEQ, 2015) that state "If credible information on toxicokinetics or toxicodynamics is available to support a lower UF than the default of 10, a UF of 3, or even 1, may be used", we recommend TCEQ consider reducing the uncertainty factors as described below.

> Interspecies Variation (UF_A). For direct acting agents causing effects at the portal of entry, variation across species is expected to be reduced since variables that typically impact systemic dose delivery (absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. Although TCEQ guidelines do not address this issue explicitly, ECETOC (2010) states that, "A default factor of 1 for interspecies extrapolation for local effects is considered to be sufficiently conservative" when establishing derived no effect level (DNEL) values. An UF_A of 1 for pMDI is justified by the nasal lesions (e.g., hyperplasia, olfactory degeneration, inflammation) induced by the inhalation of other irritants in rats and mice that were comparable in both character and severity (Gaskell 1990; Abdo et.al., 1998). Alternatively, the USEPA (2001) standard operating procedure for deriving acute exposure guideline levels (AEGLs) states, "If evidence is available indicating that the mechanism or mode of action, such as direct-acting irritation or alkylation, is not expected to differ significantly among species, an interspecies UF of 3 is generally used". In such cases, a UF_A value of 3 is sufficient to

account for both toxicokinetic and toxicodynamic variation across species. However, the RDDR adjustment already incorporates a toxicokinetic uncertainty factor of 0.68 (i.e., 1 / 1.4625). Thus, to achieve a full factor of 3 for UF_A, toxicodynamic uncertainty should not exceed a value of 4.4 (3 / 0.68).

Intraspecies Variation (UF_H). For direct acting agents causing effects at the portal of entry, variation across individuals is again expected to be reduced since variables that typically affect systemic dose delivery (absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. Although TCEQ guidelines do not address this issue explicitly, the USEPA (2001) standard operating procedure for deriving acute exposure guideline levels (AEGLs) states the following, "In those cases in which the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulations is unlikely to differ, an intraspecies UF of 3-fold is generally used. Typically, this response involves a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role." We recommend that TCEQ consider use of a factor of 3 to account for intraspecies variation (UF_H) when deriving the acute ReV for pMDI.

TCEQ Response:

The TCEQ disagrees that a simple default factor of 1 for the interspecies extrapolation of local effects is sufficiently conservative, which is why we conduct dosimetric modeling to adjust for toxicokinetic interspecies differences. Indeed, our RDDR is 0.6789 in this case; less than 1. In regard to AEGLs, they are not derived for the daily protection of the public against sensitive adverse effects, but rather for emergency situations. Even then, the AEGL methodology is not designed to protect against sensitive health effects. Given their purpose, TCEQ ReVs/ESLs are more conservatively derived to adequately protect the public against the most sensitive adverse effects of a given chemical. The commenter also states that "Thus, to achieve a full factor of 3 for UF_A, toxicodynamic uncertainty should not exceed a value of 4.4 (3 / 0.68)." The TCEQ used an uncertainty factor of 3 to adjust for potential interspecies toxicodynamic differences, consistent with this comment.

In regard to intrahuman variability, the commenter again cites the AEGL methodology, "In those cases in which the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulations is unlikely to differ, an intraspecies UF of 3-fold is generally used. Typically, this response involves a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role." Again, given the purpose of TCEQ ReVs/ESLs, they are more conservatively derived than AEGLs in order to adequately protect the public against the most sensitive adverse effects of a given chemical. For an acute ReV for a direct acting chemical where the study was not in a susceptible human subpopulation, the consideration of exercise alone suggests that a UF_H of 3 may be inadequate.

Comment 14:

Conclusion

Based on the absence of an adverse effect (i.e., cytotoxicity) in an acute inhalation study with pMDI (Pauluhn et al., 1999), ACC believes the available data support an Acute ReV of 390 µg/m^3 (rounded to two significant digits). This value is above the TCEQ-derived value of 27 µg/m^3. The difference between the ACC and TCEQ-derived values is due to TCEQ's (a) inappropriate identification of 2.4 mg/m^3 as a LOAEL even though this purportedly adverse effect was not observed during the first 60 min of exposure, the time frame targeted by the Acute (1-h) ReV, (b) inappropriate identification of an adaptive lung response (i.e., minimal pulmonary irritation) as an adverse effect, despite the absence of a truly adverse effect (i.e., cytotoxicity) in the same rat species after a longer-term exposure (6-h) to 2.4 mg/m^3 (Pauluhn. 2000), (c) derivation of an inappropriate RDDR value, and (d) selection of overly conservative uncertainty factors despite data and regulatory guidance supporting lower values. ACC believes the available data and TCEQ (2015) guidance support the derivation of a science-based ReV and take precedence over the conservative approach used to derive the Acute ReV currently proposed by TCEQ.

TCEQ Response:

The TCEQ considers an indication of irritation itself as an adverse effect. Histopathological or other additional adverse changes (e.g., cytotoxicity as cited by ACC) need not co-occur with irritation as toxicity factors should be based on mild/sensitive adverse effects such as mild irritation. The TCEQ certainly considers the 1.5-h minimal LOAEL identified for irritation/decreased tidal volume as relevant to the 1-h ReV/ESL. Neither the TCEQ nor the exposed public would agree that mild pulmonary irritation is simply an adaptive non-adverse effect in the absence of cytotoxicity. See TCEQ responses above regarding RDDRs. The acute ReV proposed by the commenter (390 µg/m^3) is significantly above even the OSHA STEL ceiling (200 µg/m^3). Based on this and considering the scientific judgments in TCEQ's own derivation, the TCEQ considers the 390 µg/m^3 proposed by the commenter as inadequate for the protection of the general public's health. By contrast, the TCEQ ReV/ESL are appropriately conservative, justified, and adequately health-protective.

Comment 15:

Identification of Health-Based Acute ReV – Vapor

Selection of Key Study – Shiotsuka et al. (2006)

As stated by TCEQ, the focus of the acute ReV is generally a one-hour exposure duration. Therefore, acute exposure studies are preferentially used to derive the acute ReVs. Acute as well as subacute studies may be used to derive the acue (1-h) ReV (i.e., if the only toxicity information for a chemical is from a well-conducted subacute study lasting from 1 day to 4 weeks, it is used to derive an acute (1-h) ReV corresponding to the desired exposure duration). TCEQ used repeated exposure studies for the derivation of the No Observed Adverse Effect Level (NOAEL) for the acute ReV. The Shiotsuka et al. (2006) study involved a 3-week exposure for 5 hours/day for 5 days/week. This study demonstrated increased squamous metaplasia and goblet cell hyperplasia in the anterior portions of the nose at 0.005 ppm, which the study authors considered to be a "subtle adaptive epithelial response to injury". The study authors set the NOAEL to 0.0175 ppm.

ACC believes that a more appropriate study for calculation of the acute vapor ReV is the Kopf (2015) 1-week exposure study conducted on HDI monomer, which is available on the ECHA website. Consideration of this study is consistent with TCEQ guidelines (§3.3.2. 2015). In the 1-week study, rats were exposed to HDI for 6 hours/day, 5 days/week for 1 week to concentrations of 0.027, 0.1, 0.46, and 1.97 ppm. According to the summary, rats exposed to 0.1 ppm displayed no substance-specific clinical signs and minimal (if any) changes in lung function and histopathology. Histopathology revealed the typical anterior-posterior gradient of irritation related injury in the nasal cavity at the two highest doses. Animals exhibited reflexively-induced changes in breathing patterns due to stimulation of the nociceptive trigeminal nerve located in the nasal cavity. The study author determined that 0.1 ppm constituted the borderline NOAEL based on effects observed in the upper respiratory tract. The NOEL of the 1-week study is 0.027 ppm. A health protective selection of the NOAEL, such as preferred by OEHHA (2016), would set the NOAEL in the 1-week study at 0.027 ppm. We believe use of the 1-week HDI exposure study provides a better surrogate for acute exposures than the 3-week study.

TCEQ Response:

The TCEQ did investigate the summary of Kopf 2015 as provided by ECHA that ACC recommends as the more appropriate study for the derivation of the acute vapor. The TCEQ agrees that Kopf 2015 is the more appropriate study for the derivation of the acute vapor ReV. Thus, the TCEQ has made Kopf (2015) the key study.

Comment 16:

Acute (1-h) ReV – MDI and HDI Vapor

Using Haber's rule as modified by ten Berge (TCEQ, 2015) with an "n" of 3 results a 1-h POD_{ADJ} of 49.06 ppb [$((27\ ppb)^3 \times (6\ h/1\ h))^{1/3}$]. As done by TCEQ (2019), the POD_{ADJ} of 49.06 ppb was adjusted to a POD_{HEC} of 49.06 ppb using the default dosimetric adjustment factor (DAF) of 1 for a Category 1 vapor. As depicted in Table 2, the POD_{HEC} of 49.06 ppb is subsequently divided by a total Uncertainty Factor (UF) of 9 [i.e., 3 for interspecies uncertainty (TCEQ, 2019) and 3 for intraspecies uncertainty (see discussion above) to yield an acute (1-h) ReV of 5.5 ppb or 38 $\mu g/m^3$ (rounded to two significant digits). The corresponding acute ESL (1-h) is 1.6 ppb or 11 $\mu g/m^3$. At a minimum, the acute ReV and ESL values should be no lower than 3.3 ppb (23 $\mu g/m^3$) and 1.0 ppb (6.9 $\mu g/m^3$), respectively, based on the TCEQ-derived POD_{HEC} (29.92 ppb) and a total UF of 9 (Table 2).

Conclusion

Based on the fact that the focus of the acute ReV is to protect against adverse effects from a 1-hour exposure, ACC believes that the more appropriate study for the derivation of the acute vapor ReV is Kopf (2015). The effects observed in the Shiotsuka et al. study are due to a 3-week repeated exposure and are therefore not likely to occur during a 1 hour exposure. While the effects observed in the 1-week Kopf study are still due to repeated exposure, the shorter time period results in more relevant effects. Therefore, ACC believes acute ReV should be 38 $\mu g/m^3$

(5.5 ppb) based on the POD of 0.027 ppm from the Kopf study and a more appropriate total uncertainty factor of 9.

TCEQ Response:

The TCEQ agrees and will use the Kopf 2015 study. However, regarding UFs the TCEQ will continue to use a UF_H of 10 for intraspecies variability (see with TCEQ's response to Comment 13).

Comment 17:

Identification of Health-Based Chronic ReV - Aerosol

POD – TCEQ Perspective

In its draft Development Support Document (DSD) for methylene diphenyl diisocyanates (MDI) and hexamethylene diisocyanate (HDI), the TCEQ (2019) identified the two-year chronic inhalation study by Reuzel et al. (1994b) as the key study and bronchiolo-alveolar hyperplasia (as reported by Feron et al., 2001) as the critical effect for derivation of the chronic ReV for pMDI / pHDI.

POD - ACC Perspective

ACC agrees that Reuzel et al. (1994b) is the key study for derivation of the chronic ReV; however, it does not agree with the critical effect upon which this value is based. As discussed in our earlier comments (ACC, 2018b), the adverse effects reported by Reuzel et al. (1994b) are limited to fibrosis and olfactory epithelial cell degeneration. In its draft document, TCEQ (2019) considered three endpoints relevant to these adverse effects but also considered five other statistically significant changes that are not adverse or precursors to these effects (Table 20). Subsequently, TCEQ selected one of the five statistically significant changes (bronchiolo-alveolar hyperplasia) for derivation of the PODHEC, despite TCEQ (2015) guidance that focuses on identifying adverse effects and warns that *"... one must be cautious in relating a statistical finding to a true adverse biological effect* ...". As discussed below, this selection is inconsistent with TCEQ guidance (2015), practice (2019) and the best use of available science.

- Hyperplasia is not an Adverse Effect. TCEQ (2015) guidance (§3.6.1. Determination of Adverse Effects) states *"(a)dversity typically implies some induction of functional impairment or generation of pathological lesion(s) that affects the performance of the whole organism or reduces an organism's ability to withstand or respond to additional environmental challenges.*" Hyperplasia, an increase in the number of normal cells, does not meet this definition and can best be classified as an adaptive response, one of the characteristics of Non-Adverse Effects listed by TCEQ (§3.6.1.4.1). Nowhere in the TCEQ (2015) guideline is hyperplasia associated with an adverse effect. Indeed, Table B-1 of same states that USEPA and CA OEHHA categorize hyperplasia as a NOAEL. Consistent with its own guidelines, CA OEHHA selected pulmonary interstitial fibrosis as the critical

effect in rats exposed to pMDI via inhalation when it derived its chronic Reference Exposure Level (REL) for MDI (OEHHA, 2016).

- Hyperplasia is not a precursor to an Adverse Effect. This same section of TCEQ guidance allows a "biologically significant precursor lesion" to be considered an adverse effect "only if it is an immediate precursor of the toxic effect." This exception was "seemingly" used by TCEQ (2019) to classify as adverse the adaptive response (decreased tidal volume) caused by < 60 min exposures to high, cytotoxic concentrations of pMDI (15.8 or 38.7 mg/m^3). However, bronchiolo-alveolar hyperplasia is neither an adverse effect nor a precursor to the adverse lung effects (i.e., fibrosis, olfactory cell degeneration) reported by Reuzel et al. (1994b).

- Hyperplasia from HDI vapor was not considered adverse. Consistent with their policies, when the USEPA (1994) and TCEQ (2019) reviewed the inhalation study (Shiotsuka et al., 1989) used to derive the RfC and chronic ReV for HDI vapor, respectively, both agencies used the NOAEL for degeneration of the olfactory epithelium as the critical adverse effect, considering other nasal effects (e.g., hyperplasia / metaplasia, inflammation) to be adaptive effects, rather than adverse effects.

Consistent with TCEQ guidance (2015), ACC believes the POD should be based on an adverse effect or an immediate precursor lesion. TCEQ (2019) Table 20 lists three candidate adverse effects: localized fibrosis (both sexes) with a POD value of 0.766 mg/m^3, interstitial fibrosis (females only) with a POD of 0.314 mg/m^3 and olfactory epithelial cell degeneration (both sexes) with a POD value of 1.17 mg/m^3. ACC considers these three adverse effects as reasonable candidates for chronic ReV derivation.

TCEQ Response:

Fibrosis and olfactory epithelial cell degeneration are endpoints that are serious in nature and not the mild/sensitive adverse effects preferred for the derivation of toxicity factors to protect public health. If there were no alternatives, a more conservative evaluation would be necessary to derive a chronic ReV/ESL based on these more severe endpoints (e.g., a $BMCL_{01}$, not $BMCL_{10}$, was used for silicosis). However, that is not necessary in this case. Moreover, the DSD does not characterize hyperplasia as adverse, but rather a "mild" or "sensitive" effect (see Section 4.1.4.4). While the approach may be viewed as a departure from the norm, DSDs are developed on a case-by-case basis exercising best professional judgment. In this case, the TCEQ selects a sensitive effect occurring at benchmark HEC doses just below those for more serious adverse effects. The critical effect is a sensitive effect that may or may not be characterized as mildly adverse (see Table b-1 of TCEQ 2015) but just precedes more serious adverse effects on the continuum of PMDI-induced respiratory tract effects. Thus, the TCEQ is not being unduly conservative. Information to this effect has been added to the DSD.

Comment 18:

POD_{ADJ} Derivation

TCEQ adjusts POD values for exposure duration and frequency (POD_{ADJ}) by multiplying factors of (6/24 hours/day) and (5/7 days/week) for a total adjustment of 0.1786. For the three adverse effects above, the POD_{ADJ} values (Table 2) are 0.1368 mg/m^3 (localized fibrosis), 0.0561 mg/m^3 (interstitial fibrosis), and 0.2090 mg/m^3 (olfactory epithelial cell degeneration).

This adjustment reflects the default assumption that adverse effects are attributable to cumulative exposure (i.e., AUC or C x T as a dose measure). This approach assumes Haber's law holds true for the nasal and pulmonary effects of MDI. The applicability of Haber's law to sensory irritation has been reviewed for multiple chemicals (Shusterman et al., 2006). The data suggest that for sensory irritants deviations from Haber's law do occur in which the concentration term is a more important determinant of response than time. In such cases, the peak concentration or a weighted cumulative dose (e.g., CnxT) serves as a more appropriate dose-metric than AUC. Although there are insufficient data to conduct a quantitative analysis for MDI with respect to the relative importance of concentration vs. time for a given tissue response, the similarity between acute, subchronic, and chronic effect levels for MDI is consistent with an assumption that the point of contact effects of MDI are driven more by concentration than time/duration. Thus, this exposure-duration / -frequency adjustment may be overly conservative by a factor of as much as 5.6-fold (i.e., 1/0.1786), an effect that should reduce the need for TCEQ to adopt such conservative values at other decision points in the ReV derivation process.

TCEQ Response:

The commenter acknowledges that there are insufficient data to conduct a quantitative analysis for MDI with respect to the relative importance of concentration vs. time for a given tissue response. Accordingly, the TCEQ's adjustments were appropriate. Additionally, if data are insufficient to directly justify deviation from the default duration-adjustment approach, they are certainly insufficient to indirectly justify deviation from the norm in other areas of the assessment (e.g., mere possible conservatism in one area does not adequately justify less conservatism in another, especially where it would involve deviation from best judgment for an issue for which the referenced information is not even relevant). The TCEQ's goal throughout the process is to make the best decision possible at each decision point given the information directly relevant to that particular decision.

Comment 19:

POD_{HEC} and RDDR Derivation

As described by TCEQ (2019), the POD_{HEC} is derived by multiplying the POD_{ADJ} by the Regional Deposited Dose Ratio (RDDR). Using the most current version of the MPPD software (v3.04), ACC was able to duplicate in large part the human (Figure 5) and rat (not shown) Deposition Fractions (DF) modeled by TCEQ. However, as with the Pauluhn et al. (1999) study above, TCEQ adjusted the MPPD default ventilation based on body weights of the rats on study using USEPA (1994) methodology but did not similarly adjust the model defaults for other respiratory parameters (i.e., FRC, head volume, lung region surface areas). ACC made these adjustments using the TCEQ-calculated body weights for female rats (BW = 301.5 g) and male + female rats

(BW = 412.25 g); the model outputs are depicted in Figure 6 (female rats) and Figure 7 (male + female rats).

TCEQ Response:

As described above, in the absence of study- or model-specific data, defaults were used for all of the parameters that were not provided. These defaults are found in updated USEPA guidance (USEPA 2012) and are commonly used in risk assessments.

Comment 20:

Chronic ReV Derivation – Reuzel (1994b)

Chronic ReV and ESL values for pMDI aerosol are presented in Table 2 using POD values identified by either TCEQ (2019) or ACC; data used by TCEQ and ACC are provided in black and red text, respectively. The Chronic ReV derived by TCEQ was 1.8 µg/m^3; Chronic ReV values (rounded to two significant digits) derived by ACC (Table 2) range from 13 µg/m^3 (interstitial fibrosis) to 26 µg/m^3 (localized fibrosis).

ACC agrees with the database uncertainty factor (UF_D) of 1 and the interspecies uncertainty factor (UF_A) of 3 selected by TCEQ, although ACC uses a different format to express the UF_A of 3 (see above under Acute ReV derivation). However, ACC again believes the TCEQ intraspecies uncertainty factor (UF_H) of 10 is overly conservative for a direct acting agent like pMDI that causes effects at the portal of entry. For such agents, variation across individuals is expected to be reduced since toxicokinetic variables that typically affect systemic dose delivery (i.e., absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. This position is supported by results of occupational studies (DFG, 1997) summarized by TCEQ (2019) that reported no significant changes in lung spirometry at MDI/pMDI concentrations below 200 ug/m^3 or increases in respiratory symptoms at 50 ug/m^3 or less. Thus, as stated above, ACC agrees with USEPA (2001) and recommends an UF_H of 3 to account for intraspecies toxicodynamics.

TCEQ Response:

In regard to intrahuman variability, given the purpose of TCEQ chronic ReVs/ESLs, they are more conservatively derived than acute AEGLs in order to adequately protect the public against the most sensitive adverse effects of a given chemical. For a chronic ReV where the study was not in a susceptible human subpopulation, the consideration of possible toxicokinetic/toxicodynamic differences (e.g., routine exercise, surfactant constituent differences, age, preexisting health conditions) suggests that a UF_H of 3 may be inadequate. The scientific burden of proof is for departure from a UF_H value of 10, which the commenter has not met and is unlikely to be able to meet.

Comment 21:

Conclusion

The analysis outlined above supports the conclusion that a chronic ReV of 13 µg/m^3 – 38 µg/m^3 (rounded to two significant digits) will not cause respiratory tract lesions in humans chronically exposed to MDI. This conclusion is consistent with results of occupational studies (DFG, 1997) summarized by TCEQ (2019) that reported no significant changes in lung spirometry at MDI/pMDI concentrations below 200 ug/m^3 or increases in respiratory symptoms at 50 ug/m^3 or less. The health-protective concentration of 50 µg/m^3 in an occupational setting is equivalent to a continuous exposure of 12 µg/m^3 (50 µg/m^3 × 8 h/24 h × 5 d/7 d) in a residential setting. This value is comparable to the lowest chronic ReV derived from an adverse effect by ACC. Thus, ACC recommends adopting chronic ReV and ESL values of 13 µg/m^3 and 3.9 µg/m^3, respectively. These health-protective values exceed the corresponding draft TCEQ values of 1.8 µg/m^3 and 0.55 µg/m^3, respectively. The difference between the ACC and TCEQ-derived values is due to the TCEQ (a) identification of adaptive respiratory tract changes as adverse despite its own guidance and practice to the contrary, (b) derivation of a lower DFA by TCEQ use of an earlier version (v3.0) of the MPPD software, and (c) selection of overly conservative UF_H despite data and regulatory guidance supporting lower values. ACC believes the available data and TCEQ (2016) guidance support the derivation of a science-based ReV and take precedence over the conservative approach used to derive the chronic ReV currently proposed by TCEQ.

TCEQ Response:

An occupational value, simply duration adjusted to an environment concentration without consideration of potentially sensitive subpopulations, is an inadequate basis for setting an adequately health-protective chronic ReV/ESL. Despite this, the commenter goes on to recommend even higher ReV values, with the upper end of the range (38 µg/m^3) being remarkably similar to occupational values from ACGIH, NIOSH, and DFG (all 50 µg/m^3). The TCEQ considers the proposed values inappropriate and insufficiently conservative for the protection of the general public.

Comment 22:

Identification of Health-Based Chronic Reference Value (ReV) - Vapor

TCEQ (2019) based its Chronic ReV for MDI / HDI vapor on a whole-body inhalation study in which Fischer 344 rats were exposed to HDI vapor at concentrations of 0, 0.005, 0.025 or 0.164 ppm for 6 h/day, 5 days/wk for two years (Shiotsuka et al., 1989). HDI-related histopathological changes were limited to the nasal cavity and included hyperplasia / metaplasia, mucous hyperplasia, inflammation and olfactory epithelial cell degeneration. The last change was judged an adverse effect. TCEQ used the study NOAEL of 0.005 ppm and a default dosimetric adjustment factor for a Category 1 vapor of 1 to derive a PODHEC of 0.8929 ppb (6.14 µg/m^3). The POD_{HEC} was divided by a total UF of 30 to yield a chronic ReV of 0.21 µg/m^3. As stated above, the UF_H of 10 included in the combined UF of 30 is excessive, particularly for such a reactive, portal of entry toxin that affects the nasal cavity where toxicokinetic factors will have a minor, if any, role in the degeneration observed. ACC recommends that the TCEQ consider a combined UF of 9 (3 each for inter- and intra-species variation) that results in chronic ReV and ESL values of 0.68 µg/m^3 (0.099 ppb) and 0.20 µg/m^3 (0.030 ppb), respectively.

TCEQ Response:

In regard to intrahuman variability, where the study was not in a susceptible human subpopulation, the consideration of possible toxicokinetic/toxicodynamic differences (e.g., routine exercise, age, preexisting health conditions) suggests that a UF_H of 3 may be inadequate. The scientific burden of proof is for departure from a UF_H value of 10, which the commenter has not met. TCEQ's UF_H of 10 is the same as that used by ATSDR (1998) and USEPA (1994), who also used nasal effects as the critical effects.

Appendix – Comments received from the American Chemistry Council (ACC) on July 19, 2019.

July 19, 2019

Submitted Via Electronic Mail

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Re: Proposed DSD: Methylene Diphenyl Diisocyanate (MDI) and 1,6-Hexamethylene Diisocyanate (HDI), All Isomers

Dear Dr. Honeycutt,

The American Chemistry Council Diisocyanates Panel[1] and Aliphatic Diisocyanates Panel[2] ("hereafter collectively referred to as "ACC") appreciate the opportunity to provide the Texas Commission on Environmental Quality (TCEQ) the following comments on the Proposed Development Support Document for Methylene Diphenyl Diisocyanate (MDI) and 1,6-Hexamethylene Diisocyanate (HDI), all isomers, dated March 6, 2019.

TCEQ has proposed values for MDI and HDI in the aerosol/particulate matter phase and values for MDI and HDI in the vapor phase. These reference values (ReVs) and effects screening levels (ESLs) are used by TCEQ for review of ambient air monitoring data and air permitting. The following table summarizes the proposed TCEQ values compared to the values ACC recommends and believes are health-protective, supported by the weight of scientific evidence, and consistent with existing occupational exposure limits.

	TCEQ MDI and HDI Aerosol	**ACC** MDI and HDI Aerosol	**TCEQ** MDI and HDI Vapor	**ACC** MDI and HDI Vapor
Acute ReV ($\mu g/m^3$)	27	390	6.9	38
Acute ESL ($\mu g/m^3$)	8.1	120	2.1	11
Chronic ReV ($\mu g/m^3$)	1.8	13	0.21	0.68
Chronic ESL ($\mu g/m^3$)	0.55	3.9	0.063	0.20

[1] The Diisocyanates Panel represents the U.S. companies that manufacture or import methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI).

[2] The Aliphatic Diisocyanates Panel represents the U.S. companies that manufacture or import hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI) and methylene dicyclohexyl diisocyanate (H_{12}MDI).

In summary, ACC believes TCEQ should:

- Base ReVs on (a) adverse effects or immediate precursors to an adverse effect as outlined by TCEQ (2015) rather than statistically-significant physiological responses or transient adaptive changes, and (b) the weight of evidence from all studies, both short-term and long-term. The adverse effect selected by TCEQ should be accompanied by a brief rationale focused on these considerations.

- Provide a transparent basis for the variables used by TCEQ for its Regional Deposited Dose Ratio (RDDR) calculations and MPPD model exercise such as (a) MPPD version, (b) rationale for human minute volume, tidal volume and breathing frequency, and lung region surface areas that ignore current US EPA (2004, 2011) recommendations, (c) explain why TCEQ adjusted animal breathing frequency for study-specific animal body weights but no other respiratory parameters (e.g., functional residual capacity, head volume, pulmonary surface area) as allowed by the current MPPD model and/or published by the model developers (Miller et al., 2014), and

- Revise the intraspecies uncertainty factor from 10 to 3 as recommended by EPA (2001) for highly reactive chemicals that cause portal of entry effects and to better align ReVs with available epidemiological data.

Thank you for the opportunity to provide comments. ACC requests an opportunity to meet with TCEQ to discuss our comments in more detail and to address any clarifying questions. We look forward to continuing to work with TCEQ to help inform any potential future regulatory decisions on isocyanates. If you have any questions or require additional information, please contact me at sahar_osman-sypher@americanchemistry.com or 202-249-6721.

Sincerely,

Sahar Osman-Sypher
Director, Diisocyanates and Aliphatic Diisocyanates Panels

Attachment: Comments on the Proposed Acute and Chronic ReVs and ESLs for MDI and HDI

Identification of Health-Based Acute (1-hour) ReV - Aerosol

In its draft Development Support Document (DSD) for 4,4-methylene diphenyl diisocyanate (MDI) and 1,6-hexamethylene diisocyanate (HDI), the TCEQ (2019) reviewed available inhalation studies on aerosols of both substances and identified two key studies (Pauluhn et al., 1999 for MDI; Lee et al., 2003 for HDI) suitable for Point of Departure (POD) selection and Acute (1-h) Reference Value (ReV) derivation. TCEQ subsequently decided Pauluhn et al. (1999) was the better of the two studies for these purposes. ACC agrees with the selection of 2.4 mg/m^3 as a candidate point of departure (POD) but believes Pauluhn at al. (1999) may not provide the best support for this value without a rationale from TCEQ as to why an adaptive change in tidal volume represents an adverse effect or is an immediate precursor to same (TCEQ, 2015).

pMDI POD - Pauluhn et al. (1999)

Groups of male Wistar rats (n = 6) were exposed to conditioned air for 30 min followed by a 150 min exposure to pMDI aerosol at one of five concentrations (0, 2.4, 6.7, 15.8, or 38.7 mg/m^3). During this time, respiratory parameters (respiratory rate and tidal volume) were averaged over 1-min intervals. Data were normalized to the mean of the 30-min pre-exposure period which was assigned a value of 100%. Pauluhn et al. (1999) reported that respiratory rates at 2.4 and 6.7 mg/m^3 were indistinguishable from the air control group, while rates in the two highest exposure groups were ~20% higher than pre-exposure control. In contrast, concentration-dependent effects on tidal volume were observed; Figure 2 from Pauluhn et al. (1999) depicting these data is reproduced below for ease of reference.

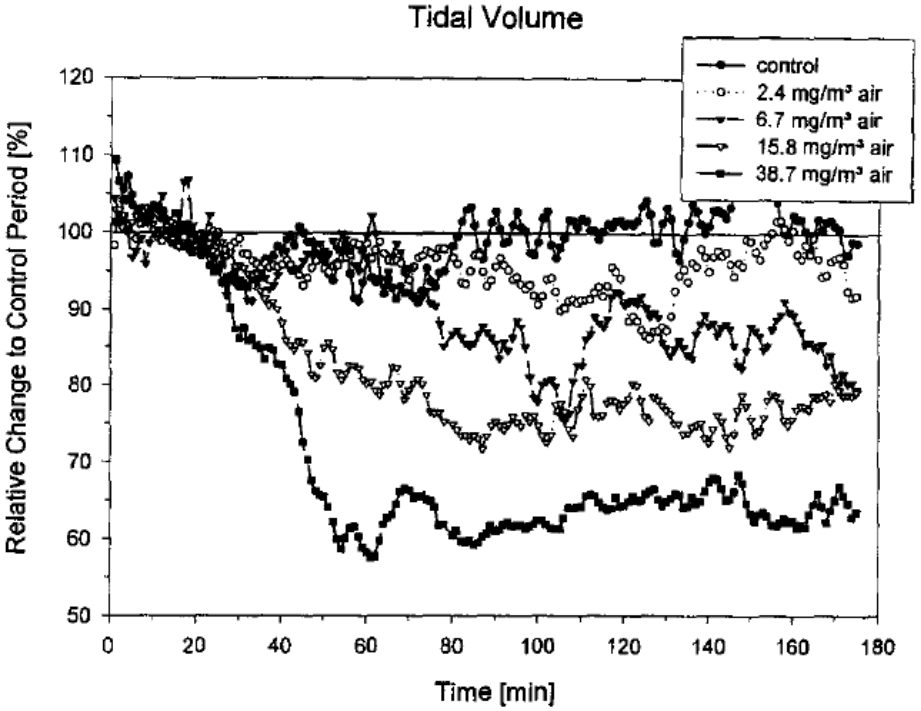

FIGURE 2. Analysis of concentration dependence of tidal volume. After acclimatization, the rats (n = 6) were exposed for 30 min to air (collection of baseline data). Subsequently the rats were exposed to PMDI for 150 min.

For the time frame relevant to an Acute (1-h) ReV, the concentration of 2.4 mg/m^3 is best described as a NOEL, not the LOAEL identified by TCEQ (2019), for the following reasons.

- First, the data in Figure 2 above clearly show that during the first 60 min of exposure to pMDI, the time frame targeted by an Acute (1-h) ReV, the tidal volume measured at 2.4 mg/m^3 is indistinguishable from control. While tidal volumes at 2.4 mg/m^3 after 60 min are observed to decrease randomly to values 0 – 15% below the corresponding control values, this result is precisely what would be predicted for a reactive aerosol that gradually begins to overwhelm natural defense mechanisms in the airways, eventually leading to a subtle, non-adverse decrease in tidal volume.

- Second, TCEQ provides no rationale for its position that this minimal adaptive / reflexive change in tidal volume after 1-h of exposure is either adverse or an "*immediate precursor"* (TCEQ, 2015) to an adverse effect. Indeed, as discussed in our earlier comments (ACC, 2018a), adverse effects (i.e., cytotoxicity) at 2.4 mg/m^3 are not seen even after an exposure duration of 6 h (Pauluhn, 2000), although they can occur at higher concentrations (3.3 – 7.2 mg/m^3) when daily 6-h exposures are extended over a two-week to 13-week period (Reuzel et al., 1994a; Pauluhn et al., 1999; Kilgour et al., 2002).

  As summarized in our earlier comments (ACC, 2018a), these studies exhibited relatively consistent NOAELs that ranged from 2.4 mg/m^3 for one 6-h exposure to ≥ 1.4 mg/m^3 for 65 daily 6-h exposures and provide a rich dataset from which to select a POD. However, in the process of identifying a suitable POD, TCEQ ignores results from longer exposure duration studies despite its guidance (TCEQ, 2015) that states "*It is acceptable risk assessment practice to incorporate longer-term data from toxicity studies to develop acute toxicity values corresponding to shorter duration exposures when it is justified by the MOA analysis"*. As outlined by TCEQ (2019) and detailed by Pauluhn (2011), MDI-induced pulmonary toxicity is initiated at points of pMDI deposition in the respiratory tract where it readily reacts with macromolecular nucleophiles (e.g., glutathione, peptides, tissue proteins). As the local nucleophilic capacity is overwhelmed and surfactant becomes increasingly dysfunctional, cytotoxicity and inflammation can ensue. On an acute scale, these effects can be seen as increases in lung weight as well as BALF levels of intracellular enzymes (LDH, γ-GT), plasma protein (ACE) and inflammatory cells. On a chronic scale, when the acute effects become biologically significant, they are manifested as olfactory epithelial cell degeneration in the nasal cavity and pulmonary fibrosis. Thus, the pMDI concentrations in subchronic studies that do not induce histopathological lesions in the respiratory tract provide critical information that can help differentiate homeostatic changes from adverse effects. Because histopathological examinations are typically conducted only in subchronic studies, the 13-wk studies by Reuzel et al. (1994a) with pMDI should be considered among the studies used to derive an acute ReV. The NOAEL of 1.4 mg/m^3 reported by Reuzel et al. (1994a) based on the absence of histological changes in the respiratory tract and lung weight changes is conservative. As stated by the authors "*… the "no-observed-adverse-effect level" of polymeric MDI was 1.4 mg/m^3, the actual no-adverse-effect level being lower than but most probably very close to 4.1 mg/m^3."* The weight of evidence from multiple acute to subchronic studies with pMDI do not support a 1-h LOAEL of 2.4 mg/m^3.

POD_{HEC} and RDDR Calculations - Pauluhn et al. (1999)

The human equivalent POD concentration (POD_{HEC}) was derived by multiplying the TCEQ-identified POD for pMDI aerosol in rats (2.4 mg/m^3) by the Regional Deposited Dose Ratio (RDDR). As shown below, the RDDR is calculated using human and animal inputs for minute ventilation (VE), deposition fraction (DF) and normalizing factor (NF) for the region(s) of interest, where NF is commonly based on the surface area of the lung region(s) of interest. The TCEQ used the Multi-Path Particle Dosimetry (MPPD) model to derive the human and animal DF values. ACC has three concerns with the TCEQ RDDR calculation.

First, TCEQ provides no rationale for its human minute volume (VE_H) of 13,800 ml/min. Apparently, this value comes from USEPA (1994) where it is listed as the default VE_H used in an earlier version (Version 2.2) of the MPPD software. However, the MPPD software has been repeatedly revised over the past 25 years and version 2.2 is no longer available. Default inputs for the human deposition model (Yeh and Schum) used in the most current version (v3.04) of the MPPD model are a breathing frequency of 12/min and a tidal volume of 625 ml; these values result in a VE_H of 7,500 ml/min, not 13,800 ml/min. However, a VE_H of 7,500 ml/min approximates that of a resting individual and may underestimate the VE_H of the human receptor population the acute ReV is designed to protect. ACC believes the VE_H for a 24-h day should be based on a respiratory rate approaching that associated with light activity, which would reflect a balance between time spent sleeping and performing heavy activities. Using long-term human inhalation rates recommended by USEPA (2011; Table 6-1) for 13 age groups between birth and 81 years of age, the latter value corresponding to the average lifespan[3] for the receptor population of interest, a mean age-weighted inhalation rate of 14.51 m^3/day can be derived. This value corresponds to a VE_H of 10,080 ml/min and a tidal volume of 630 ml (10,080 ml/min ÷ 16 breaths/min). The breathing frequency of 16/min falls halfway between human breathing frequencies (USEPA, 2004) associated with rest (12/min) and light exercise (20/min) and is comparable to that used by TCEQ (16.43/min). When these receptor-specific values are used in the MPPD human model, the resulting human Deposition Fraction (DF_H) is 0.1675 (Figure 1). ACC believes the VE_H of 10,080 ml/min is not only health protective, falling just below a VE_H of 12,160 ml/min[4] for individuals spending the whole day performing light activities, but it also provides a stronger scientific basis for derivation of regulatory air concentration limits than an unsupported default value.

Second, although TCEQ provides a reasonable rationale for use of MPPD's Long-Evans (L-E) Asymmetric deposition model, its implementation of the model is incomplete. The L-E model is based on a 330 g rat, while the mean body weight of the Wistar rats used by Pauluhn et al. (1999) is 31% lower (228 g). Although TCEQ appropriately lowered the L-E model's default tidal volume (2.06 ml) to correspond to that of the smaller Wistar rats (1.634 ml[5]), it did not similarly adjust other default respiratory parameters such as Functional Residual Capacity (FRC, 4.0 ml) and Head volume (0.42 ml). Using the scaling function incorporated into the MPPD Sprague-Dawley model[6], the FRC and Head volume for a 228 g Wistar rat were determined to be 2.99859 ml and 0.34313 ml, respectively[7]. When the L-E Asymmetric model is run with the smaller FRC and Head volumes, the rat Deposition Fraction (DF_A) for the tracheobronchial and pulmonary regions is 0.0829 (Figure 2).

Third, the human and rat NF values for the combined tracheobronchial and pulmonary regions are inappropriate. The NF_H value of 543,200 cm2 is the default value provided by USEPA (1994) based on publications by Mercer et al. (1994a, 1994b). However, USEPA (2004) currently recommends a value of

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[3] The Social Security Administration (https://www.ssa.gov/oact/STATS/table4c6.html) indicates the average US life expectancy at birth for males (76.04 years) and females (80.99 years) is 78.5 years.

[4] Using the short-term inhalation rates for the 13 age groups (Table 6-2; USEPA, 2011), individuals participating in light activities for a full 24-h day would have a mean age-adjusted inhalation rate of 12,160 ml/min (17.15 m^3/day), while resting individuals would have a mean age-adjusted inhalation rate of 4,760 ml/min (6.85 m^3/day). For comparison, the Yeh and Schum human model defaults (i.e., 12 breaths/min, tidal volume of 625 ml) yields an inhalation rate of 7,500 ml/min (10.8 m^3/day), a value between those for resting and lightly active individuals.

[5] 166.69 ml/min ÷ 102 breaths/min (L-E model default comparable to 100/min reported for rats by Inglis, 1980).

[6] Reasonable given that both the L-E and Sprague-Dawley strains are descended from the Wistar rat.

[7] Not unexpectedly given the smaller size of the rats used by Pauluhn, values for FRC, Head volume and NF_A are 6.4% - 25% lower than the model defaults for the larger L-E rat.

576,420 cm^2 based on human morphology given by Yeh and Schum (1980), *developers of the human deposition model incorporated into the MPPD software*. TCEQ also used the default NF_A value (3422.5 cm^2) listed by USEPA (1994) for the surface areas of the tracheobronchial and pulmonary regions of rats without any adjustment for the small size of rat used in the Pauluhn study. The NF_A for a 228 g rat is 3,204.1 cm^2 based on equation [56.982*(BW)^0.74213] published by the MPPD model developers (Miller et al., 2014)[5]. When these DF values are combined with human- and rat-specific variables discussed above, the resultant RDDR is 1.4724. Using the revised RDDR and a POD_{ADJ} of 2.4 mg/m^3, the human equivalent POD concentration (POD_{HEC}) is 3.5338 mg/m^3 (Table 1).

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

TCEQ RDDR = [166.69 mL/min / 13,800 mL/min] x [0.0596/0.1683] x [543,200 cm^2/3,422.5 cm^2]

TCEQ RDDR = 0.6789

ACC RDDR = [166.69 mL/min / 10,080 mL/min] x [0.0829/0.1675] x [576,420 cm^2/3,204.1 cm^2]

ACC RDDR = 1.4724

Figure 1. Human Output with MPPD v3.04 (Pauluhn et al., 1999) – ACC Inputs (Inhalability On)

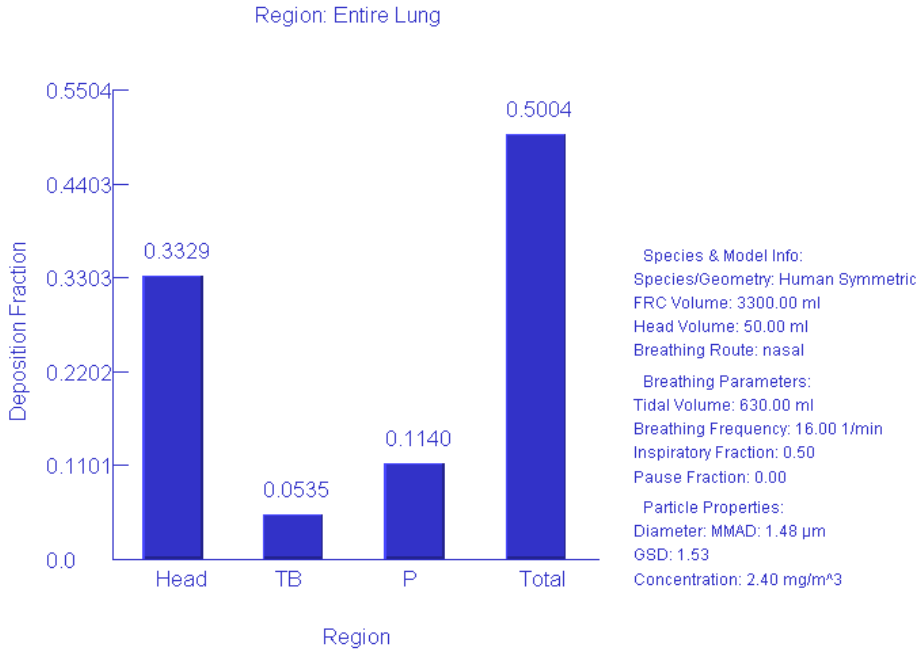
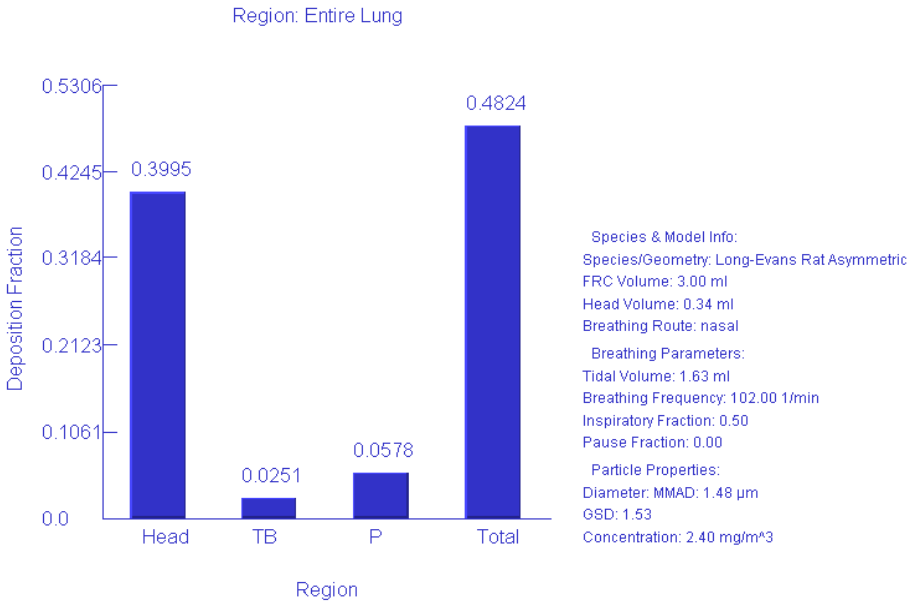


Figure 2. Rat Output with MPPD v3.04 (Pauluhn et al., 1999) – ACC Inputs (Inhalability On)



<u>pHDI POD - Lee et al. (2003)</u>

Groups of male C57BL/6J mice (n = 4-6) were exposed to pHDI aerosol dissolved in acetone for 5-h at one of three concentrations (0, 1.30, 10.83 mg/m^3) and examined for multiple endpoints at 0, 6, 18, 42, 90, 186 and 378 h post-exposure as summarized by TCEQ (2019). Consistent with the Pauluhn et al. (1999) data in rats, signs of pulmonary irritation (increased Penh) were seen immediately after exposure, returning to control levels at 6-h (1.30 mg/m3) and 42-h (10.83 mg/m3) post-exposure. Transient, concentration-dependent changes that resolved by study end included: increases in lung weight, lavage fluid protein, lavage fluid neutrophils and macrophages, as well as hypertrophy and hyperplasia in the terminal bronchioles and alveolar ducts. However, in the absence of data on cytotoxicity (e.g., lactate dehydrogenase), it cannot be ascertained whether these effects are adverse or simply reflect adaptive responses to the transient presence of dysfunctional surfactant caused by the deposition of diisocyanate. Such homeostatic / adaptive responses would include (a) the release of protein by lung parenchymal cells (*e.g.*, Type II cells) associated with the replacement of dysfunctional surfactant, (b) the influx of plasma protein / fluid due to a transient increase in the permeability of the alveolar-endothelial barrier caused by the increased surface tension due to the depletion of surfactant, and (c) increased cellular activity associated with these adaptive changes. Although the TCEQ (2015) recognizes that a statistically significant effect is not synonymous with an adverse effect, it determined, without accompanying rationale, that the effects noted by Lee et al. (2003) were adverse and identified the low pHDI concentration (1.30 mg/m^3) as the LOAEL.

Further support for the ACC position that effects reported by Lee et al. (2003) at 1.30 mg/m^3 were adaptive, not adverse, can be found in the studies performed by Pauluhn and Mohr (2001). In these studies, rats were exposed to pHDI 6h/day, 5 d/wk for either 2 weeks (1.2, 4.6, 16.3 or 69.2 mg/m^3) or 3 weeks (4.3, 14.7 or 89.8 mg/m^3). As summarized by TCEQ (2019, pg 18), wet lung weights, cell and protein content of bronchoalveolar lavage fluid, multiple lung function measurements, cytotoxicity (e.g., LDH, γ-GT), proliferative responses in the nasal and bronchiolo-alveolar regions, inflammation, and fibrosis were <u>not</u> seen at pHDI concentrations ≤ 4.6 mg/m^3. In addition, as described below, rats are more sensitive to the effects of pHDI than mice (Pauluhn, 2008).

POD_{HEC} and RDDR Calculations - Lee et al. (2003)

ACC was unable to replicate the MPPD outputs for humans (Figure 7) and mice (Figure 8; strain modeled by TCEQ not provided) reported by TCEQ (2019) using the current version (3.04) of the MPPD software. In the absence of body weight (BW) data from Lee et al. (2003), TCEQ used the default BW for male B6C3F1 mice of 0.0316 kg (USEPA, 1994). Using this BW and USEPA (1994) methodology, ACC determined a mouse ventilation rate of 36.3842 ml/min (not 32.9019 ml/min as calculated by TCEQ). Using the breathing frequency of 160 breathes/min selected by TCEQ (*i.e.*, comparable to the value of 163 breathes/min for mice; Inglis, 1980), the tidal volume was determined to be 0.2274 ml (not 0.20 ml). The aerosol characteristics were those from Lee et al. (2003), except that the density of the aerosol was 1.14 g/ml (Covestro, 2019), not the 1.04 g/ml used by TCEQ. Using these data along with the aerosol characteristics from Lee et al. (2003) as inputs to the most current version (3.04) of the MPPD software, the human and rat deposition fractions in the targeted tracheobronchial and pulmonary regions were 0.1203 (not 0.1222) and 0.0971 (not 0.0439), respectively (Figures 3 and 4). After changing the mouse normalizing factor (NF) from 506.5 to 503.5 to exclude contribution of the extrathoracic (ET) region, the RDDR was calculated to be 3.3354. The TCEQ-identified POD_{ADJ} of 2.223 mg/m^3 and a revised RDDR of 3.3354 results in a POD_{HEC} of 7.4146 mg/m^3.

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

TCEQ RDDR = [32.9019 mL/min / 13,800 mL/min] x [0.0439/0.1222] x [543,200 cm^2/506.5 cm^2]

TCEQ RDDR = 0.9186

ACC RDDR = [36.3842 mL/min / 10,080[8] mL/min] x [0.0971/0.1203] x [576,420[9] cm^2/503.5 cm^2]

ACC RDDR = 3.3354

[8] See rationale above
[9] See rationale above

Figure 3. Human Output with MPPD v3.04 (Lee et al., 2003) – ACC inputs (Inhalability On)

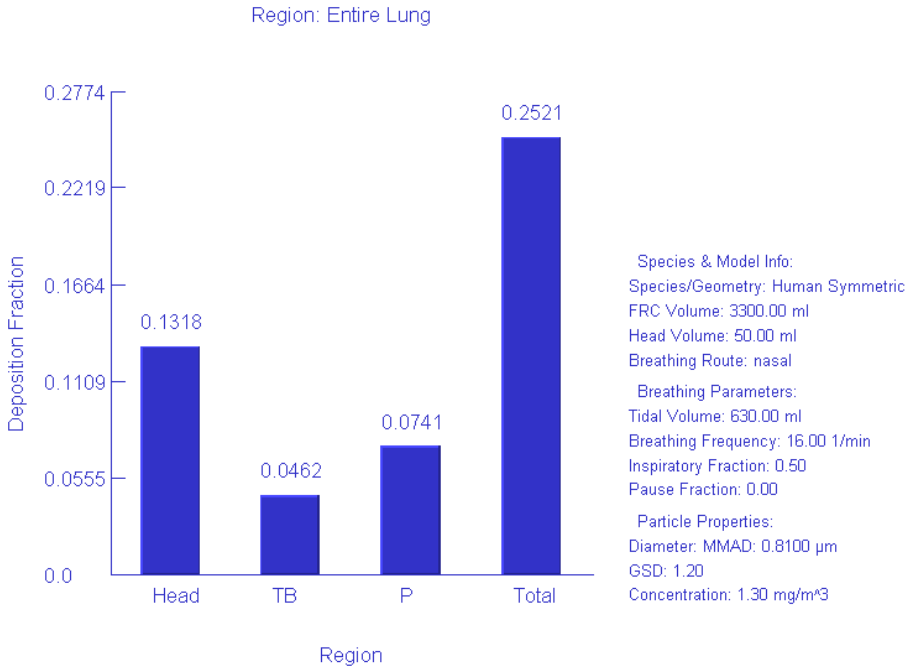
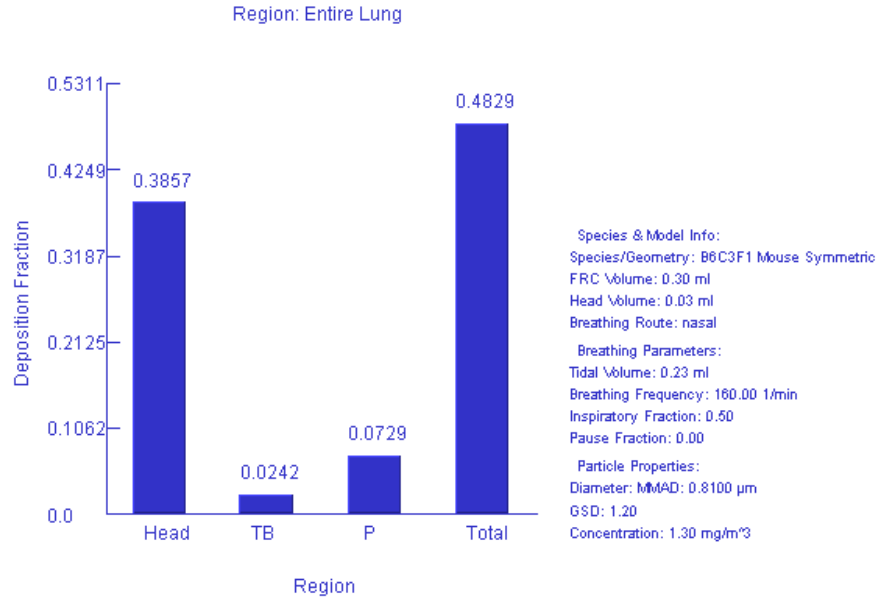


Figure 4. Mouse Output with MPPD v3.04 (Lee et al.,v2003) – ACC Inputs (Inhalability On)



<u>Selection of Key Study – Pauluhn et al. (1999) vs. Lee et al. (2003)</u>

The Acute ReV is targeted to be a concentration that is free of adverse effects when inhaled for a period of approximately 1 hour. The POD for this endpoint is best supported by results from the Pauluhn et al (1999) study. Using a series of ~60-paired measurements of tidal volume over the initial 60-min exposure period, the author demonstrated that the tidal volumes measured at a pMDI concentration of 2.4 mg/m^3 were superimposable over that measured in control air. While a transient / minimal decrement in tidal volume is not itself adverse (see §3.6.1.4.1; TCEQ, 2015), the more significant decrements in tidal volume that occur at higher pMDI concentrations and/or longer exposure durations when pulmonary defense buffers (e.g., glutathione, surfactant) are depleted could be seen as a precursor to an adverse lung effect (e.g., cytotoxicity). As discussed by ACC (2018a), this prediction is consistent with results of an

acute (6-h) pMDI aerosol inhalation study in rats (Pauluhn, 2000) that showed adaptive effects to lung irritation at pMDI concentrations of 0.7 mg/m^3 and 2.4 mg/m^3 (NOAEL) and adverse effects (e.g., cytotoxicity) at ≥ 8 mg/m^3 (LOAEL).

Scientifically, an Acute ReV is less well supported by the Lee et al. (2003) results. First, endpoints evaluated in this study were measured at 5 hours, a time frame well outside the targeted exposure duration of 1 hour for an Acute ReV. While changes were seen at this time, it is uncertain if the effects were adverse (TCEQ position) or simply a reflection of the transient, adaptive processes associated with irritation since the study did not include any enzymatic (e.g., LDH) or histological evidence of cytotoxicity. Second, endpoint uncertainty is compounded by the fact that the current MPPD model does not include an asymmetric mouse lung model. The Deposition Fraction (DF_A) derived by ACC from the symmetric B6C3F1 mouse lung model (the B6C3F1 strain was used by TCEQ for mouse BW) may over- / under-estimate the DF_A for the asymmetric lung geometry of the C57BL/6J mice used by Lee et al. (2003). Finally, as described below, at polyisocyanate concentrations relevant to derivation of an Acute ReV (*i.e.*, ≤ 10 mg/m^3), rats are more sensitive to pMDI than pHDI.

Pauluhn (2008) exposed Wistar rats and C57BL6J mice for a period of 6-h to respirable aerosols of pHDI (free NCO content of 22.8%) at a concentration of 10 mg/m^3. As shown in Table 2 from this publication, bronchoalveolar lavage data collected 20-h post-exposure showed rats were more sensitive than mice to the effects (e.g., increases in lung weight, cytotoxicity, inflammation) induced by pHDI exposure. Under these same exposure conditions (Pauluhn, 2002), bronchoalveolar lavage data collected from Wistar rats exposed to aerosols of either pMDI (31% free NCO) or pHDI (22% free NCO) exhibited comparable adverse effects (i.e., BALF increases in total protein and ACE), although pMDI was more potent than pHDI at concentrations ≤ 10 mg/m^3 (see Figure 7) Data from these studies demonstrate that (a) rats are more sensitive than mice to effects induced by inhalation of pHDI, and (b) the effects seen in rats with pMDI occur at lower concentrations than those seen with pHDI. Thus, adverse effects observed in rats with pMDI provide a conservative (health protective) basis for derivation of an acute ReV. This conclusion is consistent with the acute POD_{HEC} value derived for pMDI in rats (3.5338 mg/m^3) being lower than that derived for pHDI in mice (7.4146 mg/m^3).

Acute (1-h) ReV Derivation – Pauluhn et al. (1999)

Table 1 presents acute ReV and ESL values for pMDI aerosol derived using variables selected by either TCEQ (black text) or ACC (red text). In addition to the alternative RDDR calculated by ACC (see above), the rationale for Uncertainty Factors (UF) chosen by ACC is provided below. The Acute (1-h) ReV (rounded to two significant digits) derived by ACC is **390 µg/m^3**; the Acute (1-h) ReV proposed by TCEQ (2019) is 27 µg/m^3.

- **LOAEL to NOAEL UF**. As discussed above, the change identified by TCEQ as adverse (i.e., minimal decrease in tidal volume) can best be described as an adaptive, non-adverse effect, particularly when compared to other relatively severe effects TCEQ considers non-adverse (§3.6.1.4.1; TCEQ, 2015). However, because the minimal decrease seen at 2.4 mg/m^3 occurs only after 1-h of exposure, this effect is best described as a NOEL for the exposure period targeted by the Acute (1-h) ReV, or at worse a NOAEL, if TCEQ can provide a rationale for its claim this change is adverse. Either way, no exposure duration adjustment would be required resulting in a POD_{ADJ} of 2.4 mg/m^3. The identification of 2.4 mg/m3 as a NOAEL is also consistent with results of a subchronic study (Reuzel et al., 1994a) in rats, more sensitive than mice to the effects of pHDI (Pauluhn, 2008), that reported daily 6-h exposures to pMDI did not cause adverse effects in the respiratory tract at a 1.4 mg/m^3. Using an admittedly conservative methodology, TCEQ (2019, pg 34) adjusted the NOAEC for HDI vapor from a subacute exposure (5 h/d, 5 d/wk for 3 weeks) to a 1-h POD. This same approach can be applied to the pMDI

NOAEC of 1.4 mg/m^3 to derive an ultra-conservative 1-h POD of 2.54 mg/m^3 [((1.4 mg/m^3)^3 x 6 h ÷ 1 h)$^{1/3}$]. Judged from either perspective, there is no justification for the TCEQ application of a 2-fold UF for LOAEL to NOAEL extrapolation.

- **UFs for Interspecies (UF_A) and Intraspecies (UF_H) Variation**

  In deriving the acute ReV for pMDI, TCEQ (2019) relied on uncertainty factors of 3 to account for interspecies variation (UF_A; considers toxicodynamic factors only since toxicokinetic differences were accounted for using the RDDR approach) and 10 to account for intraspecies variation (UF_H). Due to the mode of action for MDI (i.e., irritation at the portal of entry due to reaction of macromolecules with the parent chemical), these default values are likely to be overly conservative. Consistent with TCEQ guidelines for deriving ReVs (TCEQ, 2015) that state "*If credible information on toxicokinetics or toxicodynamics is available to support a lower UF than the default of 10, a UF of 3, or even 1, may be used*", we recommend TCEQ consider reducing the uncertainty factors as described below.

  - Interspecies Variation (UF_A). For direct acting agents causing effects at the portal of entry, variation across species is expected to be reduced since variables that typically impact systemic dose delivery (absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. Although TCEQ guidelines do not address this issue explicitly, ECETOC (2010) states that, "*A default factor of 1 for interspecies extrapolation for local effects is considered to be sufficiently conservative*" when establishing derived no effect level (DNEL) values. An UF_A of 1 for pMDI is justified by the nasal lesions (e.g., hyperplasia, olfactory degeneration, inflammation) induced by the inhalation of other irritants in rats and mice that were comparable in both character and severity (Gaskell 1990; Abdo et.al., 1998).

    Alternatively, the USEPA (2001) standard operating procedure for deriving acute exposure guideline levels (AEGLs) states, "*If evidence is available indicating that the mechanism or mode of action, such as direct-acting irritation or alkylation, is not expected to differ significantly among species, an interspecies UF of 3 is generally used*". In such cases, a UF_A value of 3 is sufficient to account for both toxicokinetic and toxicodynamic variation across species. However, the RDDR adjustment already incorporates a toxicokinetic uncertainty factor of 0.68 (i.e., 1 / 1.4625). Thus, to achieve a full factor of 3 for UF_A, toxicodynamic uncertainty should not exceed a value of 4.4 (3 / 0.68).

  - Intraspecies Variation (UF_H). For direct acting agents causing effects at the portal of entry, variation across individuals is again expected to be reduced since variables that typically affect systemic dose delivery (absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. Although TCEQ guidelines do not address this issue explicitly, the USEPA (2001) standard operating procedure for deriving acute exposure guideline levels (AEGLs) states the following, "*In those cases in which the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulations is unlikely to differ, an intraspecies UF of 3-fold is generally used. Typically, this response involves a direct-acting mechanism of toxicity in which metabolic or physiologic differences are unlikely to play a major role.*" We recommend that TCEQ consider use of a factor of 3 to account for intraspecies variation (UF_H) when deriving the acute ReV for pMDI.

Conclusion

Based on the absence of an adverse effect (i.e., cytotoxicity) in an acute inhalation study with pMDI (Pauluhn et al., 1999), ACC believes the available data support an Acute ReV of **390 µg/m^3** (rounded to two significant digits). This value is above the TCEQ-derived value of 27 µg/m^3. The difference between the ACC and TCEQ-derived values is due to TCEQ's (a) inappropriate identification of 2.4 mg/m^3 as a LOAEL even though this purportedly adverse effect was not observed during the first 60 min of exposure, the time frame targeted by the Acute (1-h) ReV, (b) inappropriate identification of an adaptive lung response (i.e., minimal pulmonary irritation) as an adverse effect, despite the absence of a truly adverse effect (i.e., cytotoxicity) in the same rat species after a longer-term exposure (6-h) to 2.4 mg/m^3 (Pauluhn. 2000), (c) derivation of an inappropriate RDDR value, and (d) selection of overly conservative uncertainty factors despite data and regulatory guidance supporting lower values. ACC believes the available data and TCEQ (2015) guidance support the derivation of a science-based ReV and take precedence over the conservative approach used to derive the Acute ReV currently proposed by TCEQ.

Table 1. Acute ReV and ESL Values Derived from Key pMDI Study (Pauluhn et al., 1999)

Parameter	**pMDI Aerosol***	
Study	Pauluhn (1999)	Pauluhn (1999)
Study Quality	High	High
Interpretor	TCEQ	ACC
Study Population	Wistar rats (male)	Wistar rats (male)
Exposure Concentrations (mg/m^3)	0, 2.4, 6.7, 15.8 or 38.7	0, 2.4, 6.7, 15.8 or 38.7
Exposure Duration (number)	2.5 h (1)	2.5 h (1)
Critical Effects	Tidal Volume (irritation)	Tidal Volume (irritation)
POD (mg/m^3)	2.4	2.4
POD_{ADJ} (mg/m^3)	2.4	2.4
RDDR (unitless)	0.6789	1.4724
POD_{HEC} (mg/m^3)	1.6294	3.5338
Total UF	60	9.0
LOAEL to NOAEL	2	1
Incomplete Database(UF_D)	1	1
*Interspecies (UF_A)- Toxicokinetics***	1	0.68
*Interspecies (UF_A)- Toxicodynamics***	3	4.4
Intraspecies (UF_H)	10	3
Acute ReV [1 h] (HQ=1) (µg/m³)	**27**	**390**
Acute ESL [1 h] (HQ=0.3) (µg/m³)	**8.1**	**120**

Key:

* TCEQ (2019) values in black, ACC values in red

**ACC combined UF_A = 3 (see text)

Identification of Health-Based Acute ReV – Vapor

Selection of Key Study – Shiotsuka et al. (2006)

As stated by TCEQ, the focus of the acute ReV is generally a one-hour exposure duration. Therefore, acute exposure studies are preferentially used to derive the acute ReVs. Acute as well as subacute studies may be used to derive the acue (1-h) ReV (i.e., if the only toxicity information for a chemical is from a well-conducted subacute study lasting from 1 day to 4 weeks, it is used to derive an acute (1-h) ReV corresponding to the desired exposure duration). TCEQ used repeated exposure studies for the derivation of the No Observed Adverse Effect Level (NOAEL) for the acute ReV. The Shiotsuka et al. (2006) study involved a 3-week exposure for 5 hours/day for 5 days/week. This study demonstrated increased squamous metaplasia and goblet cell hyperplasia in the anterior portions of the nose at 0.005 ppm, which the study authors considered to be a "subtle adaptive epithelial response to injury". The study authors set the NOAEL to 0.0175 ppm.

ACC believes that a more appropriate study for calculation of the acute vapor ReV is the Kopf (2015) 1-week exposure study conducted on HDI monomer, which is available on the ECHA website. [10] Consideration of this study is consistent with TCEQ guidelines (§3.3.2. 2015). In the 1-week study, rats were exposed to HDI for 6 hours/day, 5 days/week for 1 week to concentrations of 0.027, 0.1, 0.46, and 1.97 ppm. According to the summary, rats exposed to 0.1 ppm displayed no substance-specific clinical signs and minimal (if any) changes in lung function and histopathology. Histopathology revealed the typical anterior-posterior gradient of irritation related injury in the nasal cavity at the two highest doses. Animals exhibited reflexively-induced changes in breathing patterns due to stimulation of the nociceptive trigeminal nerve located in the nasal cavity. The study author determined that 0.1 ppm constituted the borderline NOAEL based on effects observed in the upper respiratory tract. The NOEL of the 1-week study is 0.027 ppm. A health protective selection of the NOAEL, such as preferred by OEHHA (2016), would set the NOAEL in the 1-week study at 0.027 ppm. We believe use of the 1-week HDI exposure study provides a better surrogate for acute exposures than the 3-week study.

Acute (1-h) ReV – MDI and HDI Vapor

Using Haber's rule as modified by ten Berge (TCEQ, 2015) with an "n" of 3 results a 1-h POD_{ADJ} of 49.06 ppb [$((27\ ppb)^3 \times (6\ h/1\ h))^{1/3}$]. As done by TCEQ (2019), the POD_{ADJ} of 49.06 ppb was adjusted to a POD_{HEC} of 49.06 ppb using the default dosimetric adjustment factor (DAF) of 1 for a Category 1 vapor. As depicted in Table 2, the POD_{HEC} of 49.06 ppb is subsequently divided by a total Uncertainty Factor (UF) of 9 [*i.e.*, 3 for interspecies uncertainty (TCEQ, 2019) and 3 for intraspecies uncertainty (see discussion above) to yield an acute (1-h) ReV of 5.5 ppb or 38 $\mu g/m^3$ (rounded to two significant digits). The corresponding acute ESL (1-h) is 1.6 ppb or 11 $\mu g/m^3$. At a minimum, the acute ReV and ESL values should be no lower than 3.3 ppb (23 $\mu g/m^3$) and 1.0 ppb (6.9 $\mu g/m^3$), respectively, based on the TCEQ-derived POD_{HEC} (29.92 ppb) and a total UF of 9 (Table 2).

[10] See ECHA Website: https://echa.europa.eu/registration-dossier/-/registered dossier/14852/7/6/3/?documentUUID=e000ffca-52b7-497f-a0f8-8f16072bbc4f

Conclusion

Based on the fact that the focus of the acute ReV is to protect against adverse effects from a 1-hour exposure, ACC believes that the more appropriate study for the derivation of the acute vapor ReV is Kopf (2015). The effects observed in the Shiotsuka et al. study are due to a 3-week repeated exposure and are therefore not likely to occur during a 1 hour exposure. While the effects observed in the 1-week Kopf study are still due to repeated exposure, the shorter time period results in more relevant effects. Therefore, ACC believes acute ReV should be **38 µg/m^3** (5.5 ppb) based on the POD of 0.027 ppm from the Kopf study and a more appropriate total uncertainty factor of 9.

Table 2. Acute ReV and ESL Values Derived from Key HDI Vapor Studies

Parameter	**HDI Vapor***		
Study	Shiotsuka et al. 2006	Shiotsuka et al. 2006	Kopf et al. 2015
Study Quality	High	High	High
Interpretor	TCEQ	ACC	ACC
Study Population	SD Rats (10/sex/group)	SD Rats (10/sex/group)	Wistar Rats (10/male/group)
Exposure Concentrations (mg/m^3)	0, 5, 17.5, or 150 ppb	0, 5, 17.5, or 150 ppb	0, 0.027, 0.1, 0.46, or 1.97 ppm
Exposure Duration (number)	5 h/d, 5 d/wk for 3 wk	5 h/d, 5 d/wk for 3 wk	6 h/d, 5d/wk for 1 wk
Critical Effects	Olfactory epithelial cell degeneration and chronic nasal cavity inflammation	Olfactory epithelial cell degeneration and chronic nasal cavity inflammation	Upper respiratory tract effects
POD (ppb)	17.5	17.5	27
POD_{ADJ} (ppb)	29.92	29.92	49.06
RGDR (unitless)	1	1	1
POD_{HEC} (ppb)	29.92	29.92	49.06
Total UF	30	9	9
LOAEL to NOAEL	1	1	1
Incomplete Database(UF_D)	1	1	1
Interspecies (UF_A)- Toxicokinetics	1	1	1
Interspecies (UF_A)- Toxicodynamics	3	3	3
Intraspecies (UF_H)	10	3	3
Acute ReV [1-h] (HQ=1) ($\mu g/m^3$)	6.9	23	38
Acute ESL [1-h] (HQ=0.3) ($\mu g/m^3$)	2.1	6.9	11
Acute ReV [1-h] (HQ=1) (ppb)	1.0	3.3	5.5
Acute ESL [1-h] (HQ=0.3) (ppb)	0.30	1.0	1.6

Key:

* TCEQ (2019) values in black, ACC values in red

Identification of Health-Based Chronic ReV - Aerosol

POD – TCEQ Perspective

In its draft Development Support Document (DSD) for methylene diphenyl diisocyanates (MDI) and hexamethylene diisocyanate (HDI), the TCEQ (2019) identified the two-year chronic inhalation study by Reuzel et al. (1994b) as the key study and bronchiolo-alveolar hyperplasia (as reported by Feron et al., 2001) as the critical effect for derivation of the chronic ReV for pMDI / pHDI.

POD - ACC Perspective

ACC agrees that Reuzel et al. (1994b) is the key study for derivation of the chronic ReV; however, it does not agree with the critical effect upon which this value is based. As discussed in our earlier comments (ACC, 2018b), the adverse effects reported by Reuzel et al. (1994b) are limited to fibrosis and olfactory epithelial cell degeneration. In its draft document, TCEQ (2019) considered three endpoints relevant to these adverse effects but also considered five other statistically significant changes that are not adverse or precursors to these effects (Table 20). Subsequently, TCEQ selected one of the five statistically significant changes (bronchiolo-alveolar hyperplasia) for derivation of the POD_{HEC}, despite TCEQ (2015) guidance that focuses on identifying adverse effects and warns that "*... one must be cautious in relating a statistical finding to a true adverse biological effect ...*". As discussed below, this selection is inconsistent with TCEQ guidance (2015), practice (2019) and the best use of available science.

- Hyperplasia is not an Adverse Effect. TCEQ (2015) guidance (§3.6.1. Determination of Adverse Effects) states "*(a)dversity typically implies some induction of functional impairment or generation of pathological lesion(s) that affects the performance of the whole organism or reduces an organism's ability to withstand or respond to additional environmental challenges.*" Hyperplasia, an increase in the number of normal cells, does not meet this definition and can best be classified as an adaptive response, one of the characteristics of Non-Adverse Effects listed by TCEQ (§3.6.1.4.1). Nowhere in the TCEQ (2015) guideline is hyperplasia associated with an adverse effect. Indeed, Table B-1 of same states that USEPA and CA OEHHA categorize hyperplasia as a NOAEL. Consistent with its own guidelines, CA OEHHA selected pulmonary interstitial fibrosis as the critical effect in rats exposed to pMDI via inhalation when it derived its chronic Reference Exposure Level (REL) for MDI (OEHHA, 2016).

- Hyperplasia is not a precursor to an Adverse Effect. This same section of TCEQ guidance allows a "*biologically significant precursor lesion*" to be considered an adverse effect "*only if it is an immediate precursor of the toxic effect.*" This exception was "seemingly" used by TCEQ (2019) to classify as adverse the adaptive response (decreased tidal volume) caused by < 60 min exposures to high, cytotoxic concentrations of pMDI (15.8 or 38.7 mg/m3). However, bronchiolo-alveolar hyperplasia is neither an adverse effect nor a precursor to the adverse lung effects (i.e., fibrosis, olfactory cell degeneration) reported by Reuzel et al. (1994b).

- Hyperplasia from HDI vapor was not considered adverse. Consistent with their policies, when the USEPA (1994) and TCEQ (2019) reviewed the inhalation study (Shiotsuka et al., 1989) used to derive the RfC and chronic ReV for HDI vapor, respectively, both agencies used the NOAEL for degeneration of the olfactory epithelium as the critical adverse effect, considering other nasal effects (e.g., hyperplasia / metaplasia, inflammation) to be adaptive effects, rather than adverse effects.

Consistent with TCEQ guidance (2015), ACC believes the POD should be based on an adverse effect or an immediate precursor lesion. TCEQ (2019) Table 20 lists three candidate adverse effects: localized fibrosis (both sexes) with a POD value of 0.766 mg/m^3, interstitial fibrosis (females only) with a POD of 0.314 mg/m^3 and olfactory epithelial cell degeneration (both sexes) with a POD value of 1.17 mg/m^3. ACC considers these three adverse effects as reasonable candidates for chronic ReV derivation.

POD_{ADJ} Derivation

TCEQ adjusts POD values for exposure duration and frequency (POD_{ADJ}) by multiplying factors of (6/24 hours/day) and (5/7 days/week) for a total adjustment of 0.1786. For the three adverse effects above, the POD_{ADJ} values (Table 2) are 0.1368 mg/m^3 (localized fibrosis), 0.0561 mg/m^3 (interstitial fibrosis), and 0.2090 mg/m^3 (olfactory epithelial cell degeneration).

This adjustment reflects the default assumption that adverse effects are attributable to cumulative exposure (i.e., AUC or C x T as a dose measure). This approach assumes Haber's law holds true for the nasal and pulmonary effects of MDI. The applicability of Haber's law to sensory irritation has been reviewed for multiple chemicals (Shusterman et al., 2006). The data suggest that for sensory irritants deviations from Haber's law do occur in which the concentration term is a more important determinant of response than time. In such cases, the peak concentration or a weighted cumulative dose (e.g., C^nxT) serves as a more appropriate dose-metric than AUC. Although there are insufficient data to conduct a quantitative analysis for MDI with respect to the relative importance of concentration vs. time for a given tissue response, the similarity between acute, subchronic, and chronic effect levels for MDI is consistent with an assumption that the point of contact effects of MDI are driven more by concentration than time/duration. Thus, this exposure-duration / -frequency adjustment may be overly conservative by a factor of as much as 5.6-fold (i.e., 1/0.1786), an effect that should reduce the need for TCEQ to adopt such conservative values at other decision points in the ReV derivation process.

POD_{HEC} and RDDR Derivation

As described by TCEQ (2019), the POD_{HEC} is derived by multiplying the POD_{ADJ} by the Regional Deposited Dose Ratio (RDDR). Using the most current version of the MPPD software (v3.04), ACC was able to duplicate in large part the human (Figure 5) and rat (not shown) Deposition Fractions (DF) modeled by TCEQ. However, as with the Pauluhn et al. (1999) study above, TCEQ adjusted the MPPD default ventilation based on body weights of the rats on study using USEPA (1994) methodology but did not similarly adjust the model defaults for other respiratory parameters (i.e., FRC, head volume, lung region surface areas). ACC made these adjustments using the TCEQ-calculated body weights for female rats (BW = 301.5 g) and male + female rats (BW = 412.25 g); the model outputs are depicted in Figure 6 (female rats) and Figure 7 (male + female rats). Depicted below and summarized in Table 3 are the RDDR calculations derived by:

- TCEQ using MPPD model defaults (not scaled to BW) and outdated human (NF_H) and rat (NF_A) Normalizing Factors referenced by USEPA (1994), and

- ACC using MPPD model values adjusted for BW as well as updated human (NF_H) and rat (NF_A) values from USEPA (2004), Miller et al. (2014) and Price (2018); the latter two sources are MPPD model developers. Values derived using the ACC approach are depicted in red text.

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

Localized Fibrosis (both sexes)
TCEQ RDDR = [271.03 mL/min / 13,800 mL/min] x [0.1090/0.1680] x [543,200 cm^2/3,422.5 cm^2]
TCEQ RDDR = 2.0224

ACC RDDR = [271.03 mL/min / 10,080 mL/min] x [0.1006/0.1598] x [576,420[11] cm^2/3,941.8[9] cm^2]
ACC RDDR = 2.4753

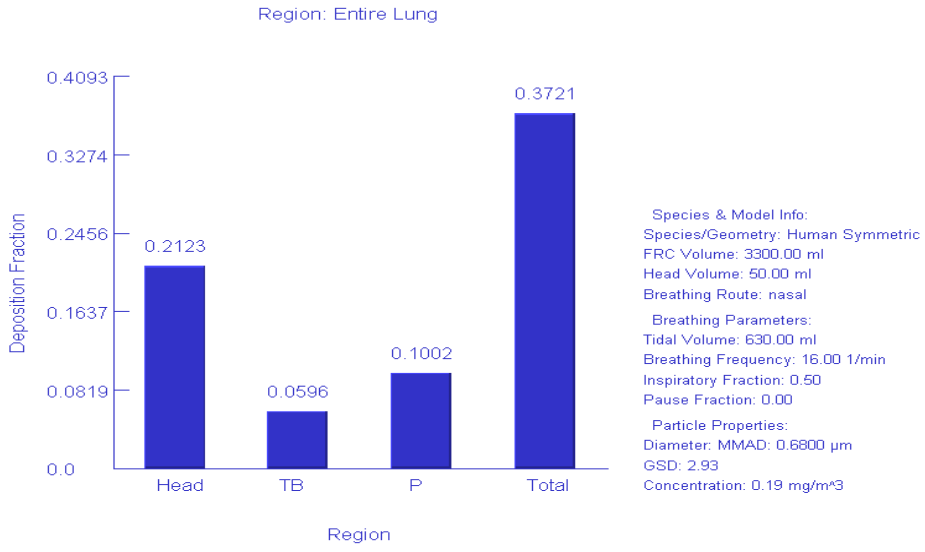
Interstitial Fibrosis (females only)
TCEQ RDDR = [209.64 mL/min / 13,800 mL/min] x [0.1000/0.1680] x [543,200 cm^2/3422.5 cm^2]
TCEQ RDDR = 1.4352

ACC RDDR = [209.64 mL/min / 10,080 mL/min] x [0.1083/0.1598] x [576,420[8] cm^2/3941.8[12] cm^2]
ACC TCEQ RDDR = 2.0612

Olfactory Epithelial Cell Degeneration (both sexes)
TCEQ RDDR = [271.03 mL/min / 13,800 mL/min] x [0.3191/0.2472] x [200 cm^2/15 cm^2]
TCEQ RDDR = 0.3380

ACC RDDR = [271.03 mL/min / 10,080 mL/min] x [0.3205/0.2123] x [303.6[8] cm^2/17.71[13] cm^2]
ACC RDDR = 0.6959

Figure 5. Human Output with MPPD v3.04 (Reuzel et al., 1994b) – Inhalability On



[11] NF_H for the surface area of either the upper respiratory tract (303.6 cm^2; Price, 2018) or pulmonary region (576,420 cm^2; USEPA, 2004) for the MPPD v3.04 human symmetric model (Yeh and Schum).

[12] NF_A for pulmonary region of a 301.5 g rat is 3,941.8 cm^2 based on equation [56.982*(BW)^0.74213] published by MPPD model developers (Miller et al., 2014).

[13] NF_A for upper respiratory tract of a 412.25 g rat is 17.71 cm^2 based on equation [0.507*(BW)^0.5901] published by MPPD model developers (Miller et al., 2014).

Figure 6. Rat (Female) Output with MPPD v3.04 (Reuzel et al., 1994b) – Inhalability On

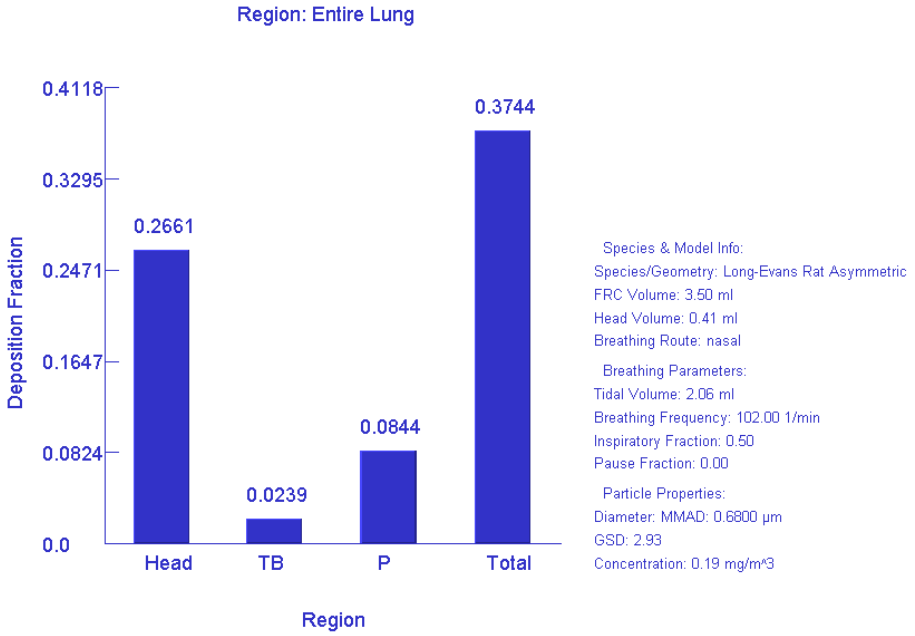
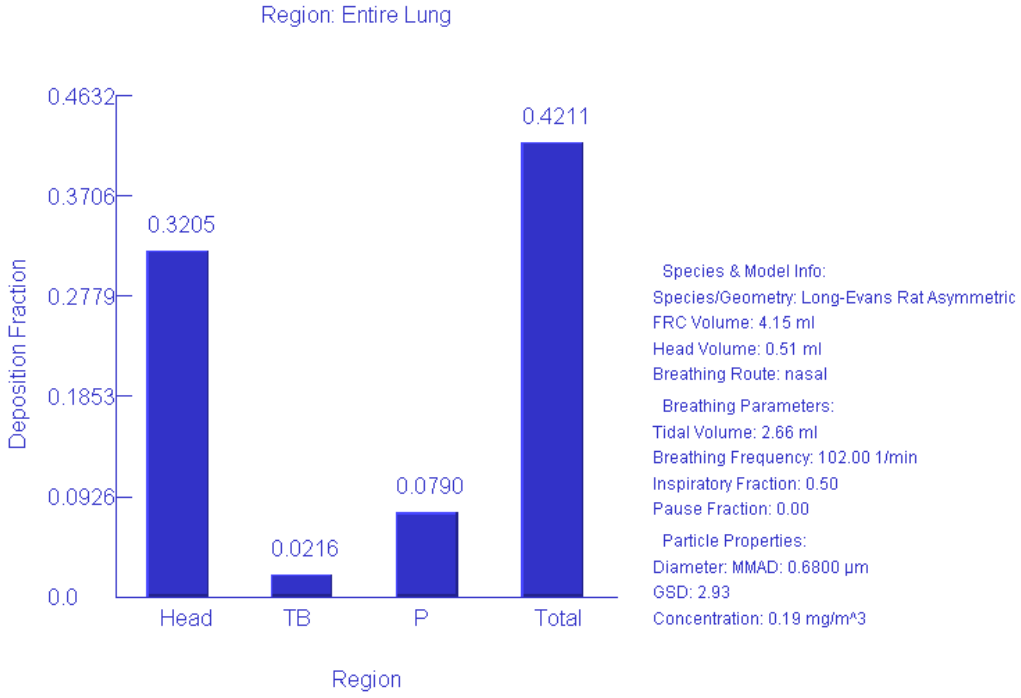


Figure 7. Rat (Male + Female) Output with MPPD v3.04 (Reuzel et al., 1994b) – Inhalability On



Chronic ReV Derivation – Reuzel (1994b)

Chronic ReV and ESL values for pMDI aerosol are presented in Table 2 using POD values identified by either TCEQ (2019) or ACC; data used by TCEQ and ACC are provided in black and red text, respectively. The Chronic ReV derived by TCEQ was 1.8 µg/m^3; Chronic ReV values (rounded to two significant digits) derived by ACC (Table 2) range from **13 µg/m^3** (interstitial fibrosis) **to 26 µg/m^3** (localized fibrosis).

ACC agrees with the database uncertainty factor (UF_D) of 1 and the interspecies uncertainty factor (UF_A) of 3 selected by TCEQ, although ACC uses a different format to express the UF_A of 3 (see above under Acute ReV derivation). However, ACC again believes the TCEQ intraspecies uncertainty factor (UF_H) of 10 is overly conservative for a direct acting agent like pMDI that causes effects at the portal of entry. For such agents, variation across individuals is expected to be reduced since toxicokinetic variables that typically affect systemic dose delivery (*i.e.*, absorption, distribution, metabolism, clearance) do not have an impact on the dose delivered at the portal of entry. This position is supported by results of occupational studies (DFG, 1997) summarized by TCEQ (2019) that reported no significant changes in lung spirometry at MDI/pMDI concentrations below 200 ug/m^3 or increases in respiratory symptoms at 50 ug/m^3 or less. Thus, as stated above, ACC agrees with USEPA (2001) and recommends an UF_H of 3 to account for intraspecies toxicodynamics.

Conclusion

The analysis outlined above supports the conclusion that a chronic ReV of **13 µg/m^3 – 38 µg/m^3** (rounded to two significant digits) will not cause respiratory tract lesions in humans chronically exposed to MDI. This conclusion is consistent with results of occupational studies (DFG, 1997) summarized by TCEQ (2019) that reported no significant changes in lung spirometry at MDI/pMDI concentrations below 200 ug/m^3 or increases in respiratory symptoms at 50 ug/m^3 or less. The health-protective concentration of 50 µg/m^3 in an occupational setting is equivalent to a continuous exposure of 12 µg/m^3 (50 µg/m3 × 8 h/24 h × 5 d/7 d) in a residential setting. This value is comparable to the lowest chronic ReV derived from an adverse effect by ACC. Thus, ACC recommends adopting chronic ReV and ESL values of **13 µg/m^3** and **3.9 µg/m^3**, respectively. These health-protective values exceed the corresponding draft TCEQ values of 1.8 µg/m^3 and 0.55 µg/m^3, respectively. The difference between the ACC and TCEQ-derived values is due to the TCEQ (a) identification of adaptive respiratory tract changes as adverse despite its own guidance and practice to the contrary, (b) derivation of a lower DFA by TCEQ use of an earlier version (v3.0) of the MPPD software, and (c) selection of overly conservative UF_H despite data and regulatory guidance supporting lower values. ACC believes the available data and TCEQ (2016) guidance support the derivation of a science-based ReV and take precedence over the conservative approach used to derive the chronic ReV currently proposed by TCEQ.

Table 3. Chronic ReV and ESL Values Derived from Reuzel et al. (1994)

Parameter	pMDI Aerosol*			
Study	Reuzel et al (1994)	Reuzel et al (1994)	Reuzel et al (1994)	Reuzel et al (1994)
Study Analysis	Feron et al (2001)	Reuzel et al (1994)	Feron et al (2001)	Reuzel et al (1994)
Study Quality	High	High	High	High
Data Interpretor	TCEQ	ACC	ACC	ACC
Study Population	Wistar rats (females, 60/group)	Wistar rats (both sexes, 60/sex/group)	Wistar rats (females, 60/group)	Wistar rats (both sexes, 60/sex/group)
Exposure Concentrations (mg/m^3)	0, 0.19, 0.98 or 6.03 (whole body)	0, 0.19, 0.98 or 6.03 (whole body)	0, 0.19, 0.98 or 6.03 (whole body)	0, 0.19, 0.98 or 6.03 (whole body)
Exposure Duration	6 h/d, 5 d/wk for 2 years	6 h/d, 5 d/wk for 2 years	6 h/d, 5 d/wk for 2 years	6 h/d, 5 d/wk for 2 years
Critical Effects	Bronchiolo-Alveolar Hyperplasia	Localized Fibrosis	Interstitial Fibrosis	Olfactory Epithelial Cell Degeneration
POD (mg/m^3)	0.216	0.766	0.314	1.170
POD_{ADJ} (mg/m^3)	0.0386	0.1368	0.0561	0.2089
RDDR	1.4351	2.4753	2.0612	0.6959
POD_{HEC} (mg/m^3)\2	0.05535	0.3386	0.1156	0.1454
Total UF	30	9	9	9
Incomplete Database(UF_D)	1	1	1	1
Interspecies (UF_A)- Toxicokinetics **	1	0.40	0.49	1.4
Interspecies (UF_A)- Toxicodynamics **	3	7.4	6.2	2.1
Intraspecies (UF_H)	10	3	3	3
Chronic $ReV_{threshold(nc)}$ (HQ=1) ($\mu g/m^3$)	1.8	38	13	16
Chronic $ESL_{threshold(nc)}$ (HQ=0.3) ($\mu g/m^3$)	0.55	11	3.9	4.8

* TCEQ (2019) values in black, ACC values in red

** ACC combined UF_A = 3 (see text)

Identification of Health-Based Chronic Reference Value (ReV) - Vapor

TCEQ (2019) based its Chronic ReV for MDI / HDI vapor on a whole-body inhalation study in which Fischer 344 rats were exposed to HDI vapor at concentrations of 0, 0.005, 0.025 or 0.164 ppm for 6 h/day, 5 days/wk for two years (Shiotsuka et al., 1989). HDI-related histopathological changes were limited to the nasal cavity and included hyperplasia / metaplasia, mucous hyperplasia, inflammation and olfactory epithelial cell degeneration. The last change was judged an adverse effect. TCEQ used the study NOAEL of 0.005 ppm and a default dosimetric adjustment factor for a Category 1 vapor of 1 to derive a POD_{HEC} of 0.8929 ppb (6.14 µg/m^3). The POD_{HEC} was divided by a total UF of 30 to yield a chronic ReV of 0.21 µg/m^3. As stated above, the UF_H of 10 included in the combined UF of 30 is excessive, particularly for such a reactive, portal of entry toxin that affects the nasal cavity where toxicokinteic factors will have a minor, if any, role in the degeneration observed. ACC recommends that the TCEQ consider a combined UF of 9 (3 each for inter- and intra-species variation) that results in chronic ReV and ESL values of **0.68 µg/m^3** (0.099 ppb) and **0.20 µg/m^3** (0.030 ppb), respectively.

Table 4. Chronic ReV and ESL Values Derived from Key HDI Vapor Studies

Parameter	**HDI Vapor***	
Study	Shiotsuka et al.1989	Shiotsuka et al.1989
Study Quality	High	High
Interpretor	TCEQ	ACC
Study Population	Fischer 344 rats (60/sex/group)	Fischer 344 rats (60/sex/group)
Exposure Concentrations (mg/m3)	0, 0.005, 0.025, or 0.164 ppm	0, 0.005, 0.025, or 0.164 ppm
Exposure Duration (number)	6 h/d, 5 d/wk for 2 years	6 h/d, 5 d/wk for 2 years
Critical Effects	Degeneration of the olfactory epithelium	Degeneration of the olfactory epithelium
POD (mg/m3)	0.005 ppm (5 ppb) (NOAEL)	0.005 ppm (5 ppb) (NOAEL)
PODADJ (mg/m3)	0.8929 ppb	0.8929 ppb
PODHEC (mg/m3)	0.8929 ppb	0.8929 ppb
Total UF	30	9
LOAEL to NOAEL	1	1
Incomplete Database (UFD)	1	1
Interspecies (UFA) - Toxicokinetics	1	1
Interspecies (UFA) - Toxicodynamics	3	3
Intraspecies (UFH)	10	3
Chronic ReV [1 h] (HQ=1) (ug/m3)	0.21 ug/m3	0.68 ug/m3
Chronic ESL [1 h] (HQ=0.3) (ug/m3)	0.063 ug/m3	0.20 ug/m3
Key:		
* TCEQ (2019) values in black, ACC values in red		

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