Manganese and Inorganic Manganese Compounds

CAS Registry Number: 7439-96-5 (except inorganic manganese compounds in the (VII) oxidation state such as permanganates)

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
°C	degrees Celsius
BMR	benchmark response
bw	body weight
d	day(s)
DSD	development support document
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
GABA	gamma-aminobutyric acid
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal

Acronyms and Abbreviations	Definition
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IOAEL	inhalation observed adverse effect level
^{acute}IOAEL	acute inhalation observed adverse effect level
^{subacute}IOAEL	subacute inhalation observed adverse effect level
$^{chronic}IOAEL_{(nc)}$	chronic inhalation observed adverse effect level (noncancer effects)
$^{chronic}IOAEL_{(c)}$	chronic inhalation observed adverse effect level (cancer effects)
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
K_{ow}	n-octanol-water partition coefficient
LC_{50}	concentration causing lethality in 50% of test animals
LD_{50}	dose causing lethality in 50% of test animals
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
LTD	limited toxicity data
mm Hg	A millimeter of mercury; approximately 1 torr, or 1/760 of standard atmospheric pressure
MOE	margin of exposure
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air

Acronyms and Abbreviations	Definition
min	minute
Mn	manganese
MOA	mode of action
MW	molecular weight
n	number
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
RD_{50}	50% reduction in respiration rate
ReV	reference value
Acute ReV	acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements
Acute ReV-24hr	acute 24-hour health-based reference value for chemicals meeting minimum database requirements
Chronic $ReV_{threshold(nc)}$	chronic health-based reference value for threshold dose response noncancer effects
RGDR	Regional Gas Dose Ratio
ROS	reactive oxygen species
RPF	relative potency factor
SA	surface area

Acronyms and Abbreviations	Definition
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
V_E	minute volume
wk	week(s)
yr	year(s)

Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of manganese (Mn), respectively, for use in air permitting and air monitoring. Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on the chemical/physical properties of Mn, and Table 4 provides a list of the applicable inorganic Mn compounds.

Table 1. Acute Health and Welfare-Based Screening Values for Mn

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated / RPF	Critical Effect(s)	Notes
Acute ReV	1 h	9.1	--	M	A	--	Inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation) in rhesus monkeys	Calculated as µg Mn/m^3
Acute ReV-24hr	24 h	5.0	--	M	A	--	Same as above.	Used for the evaluation of 24-h air monitoring data.
^{acute}ESL [a]	**1 h**	**2.7**	**--**	**P**	**S,D**	**--**	**Same as above.**	**--**
^{acute}IOAEL	6 h	1,500	--	N	none	--	Same as above.	--
^{subacute}IOAEL	--	--	--	--	--	--	--	--
^{acute}ESL$_{odor}$	--	--	--	--	--	--	--	No odor potential.
^{acute}ESL$_{veg}$	--	--	--	--	--	--	--	Insufficient data.

Bold values used for air permit reviews

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

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

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

Table 2. Chronic Health and Welfare-Based Screening Values for Mn

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Chronic $ReV_{threshold(nc)}$	70 yr	0.84	--	M	A	--	Abnormal eye-hand coordination scores in humans	Calculated as µg Mn/m³
$^{chronic}ESL_{threshold(nc)}$ [a]	**70 yr**	**0.25**	**--**	**P**	**S,D**	**--**	**Same as above.**	**--**
$^{chronic}IOAEL_{(nc)}$	70 yr	17	--	N	none	--	Same as above.	--
$^{chronic}ESL_{threshold(c)}$	--	--	--	--	--	--	--	Insufficient data.
$^{chronic}ESL_{nonthreshold(c)}$	--	--	--	--	--	--	--	Insufficient data.
$^{chronic}IOAEL_{(c)}$	--	--	--	--	--	--	--	--
$^{chronic}ESL_{veg}$	--	--	--	--	--	--	--	Insufficient data.
$^{chronic}ESL_{animal}$	--	--	--	--	--	--	--	Insufficient data.

Bold values used for air permit reviews

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

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

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

Table 3. Chemical and Physical Properties

Parameter	Value	Reference
Molecular Formula	Mn	ATSDR (2012)
Chemical Structure	Mn	ATSDR (2012)
CAS Registry Number	7439-96-5	ATSDR (2012)
Molecular Weight	54.94	ATSDR (2012)
Physical State at 25°C	solid	ATSDR (2012)
Color/Form	steel gray	ATSDR (2012)
Odor	No data	ATSDR (2012)
Synonyms	Elemental manganese, colloidal manganese, Mangan®, Cutaval®	ATSDR (2012)
Solubility in water	Decomposes	ATSDR (2012)
Log K_{ow}	No data	ATSDR (2012)
Vapor Pressure	1 Pa at 955 °C	ATSDR (2012)
Relative Vapor Density (air = 1)	No data	ATSDR (2012)
Melting Point	1,244 °C	ATSDR (2012)
Boiling Point	2,095 °C	ATSDR (2012)
Conversion Factors	1 mg Mn/m^3 = 1,000 µg Mn/m^3	

Table 4. Inorganic Manganese Compounds

Substance	CAS Number
Manganese	7439-96-5
Manganese(II) Carbonate	598-62-9
Manganese(II) Acetate	638-38-0
Manganese(IV) Oxide	1313-13-9
Manganese(III) Oxide	1317-34-6
Manganese(II,III) Oxide	1317-35-7
Manganese(II) Oxide	1344-43-0
Manganese(II) Silicate	7759-00-4
Manganese (II) Chloride	7773-01-5
Manganese(II) Sulfate	7785-87-7
Manganese(II) Nitrate	10377-66-9
Iron Manganese Oxide	11115-91-6
Manganese(II) Phosphate	14154-09-7
Manganese Dihydrogen Phosphate	18718-07-5
Ferromanganese Oxide	75864-23-2

Chapter 2 Background Information

2.1 Chemical/Physical Properties

Table 3 contains chemical/physical properties for Mn (ATSDR 2012).

2.2 Ambient Air Concentrations

Data on ambient air concentrations of Mn in Texas are available. From 2006-2015, annual averages at ambient air monitoring sites in Texas ranged from approximately 0.0012 to 0.041 µg Mn/m^3 ($PM_{2.5}$ or PM_{10}), with the percentage of nondetects ranging from 0 to 91% across monitoring sites. Maximum 24-hour (h) concentrations ranged from approximately 0.0035 to 0.34 µg Mn/m^3 (Texas Air Monitoring Information System data for 2006-2015).

Chapter 3 Acute Evaluation

In addition to deriving a 1-h acute ReV for Mn and inorganic compounds, a 24-h acute ReV was also developed. The Mn monitoring data that the TCEQ collects are based on a 24-h sampling duration. Thus, development of a 24-h acute ReV for Mn will allow the TCEQ to more fully evaluate available monitoring data.

The TCEQ will develop both acute and chronic values for Mn and inorganic compounds based on the Mn content of the compound(s) in the key studies (i.e., on a Mn equivalent basis (µg Mn/m^3)). The Mn equivalent for a given dose of an inorganic Mn compound is based on the percent of the compound's molecular weight (MW) that Mn comprises (i.e., the compound's concentration in µg/m^3 × (MW of Mn in compound / MW of compound)). From a protection of public health perspective, use of Mn equivalents assumes that other inorganic Mn compounds are equally as toxic as the compound(s) in the key study on a µg Mn/m^3 basis. This science policy decision is necessary given the lack of available studies to derive separate values for every inorganic Mn compound and is consistent with the approach of other agencies (e.g., ATSDR). However, the derived ReV and ESL values are expected to be sufficiently health-protective regardless of the inorganic environmental chemical form because they are based on the inorganic Mn compound(s) that have produced adverse effects at the lowest concentrations (i.e., the most toxic form(s) in the most sensitive species), which is the most conservative (i.e., health-protective) choice. *The toxicity factors derived in this Development Support Document (DSD), however, do not apply to organic forms of Mn or inorganic Mn compounds in the (VII) oxidation state (e.g., permanganates of: silver, calcium, ammonium, sodium, and potassium).*

3.1 Health-Based Acute ReVs and ESL

Studies in animals and humans indicate that inorganic Mn compounds have relatively low acute toxicity. An exception is potassium permanganate, which is an oxidant that can cause severe corrosion of skin or mucosa at the point of contact (ATSDR 2012). *Thus, this DSD does not apply*

to potassium permanganate or other inorganic Mn compounds in the (VII) oxidation state, or organic forms of Mn. Some subacute studies have shown that inhalation exposure to high concentrations of insoluble Mn dusts (as manganese dioxide) can cause an inflammatory response in the lung, which can lead to impaired lung function in laboratory animals (i.e., Maigetter et al. 1976, Shiotsuka 1984). However, these insoluble Mn subacute studies will not be used as key studies to derive acute ReVs because:

- This inflammatory response is characteristic of nearly all inhalable particulate matter (USEPA 1985) and not necessarily dependent upon Mn content.
- The associated free-standing, lowest-observed-adverse-effect-levels (LOAELs) are relatively high (e.g., 43-69 mg Mn/m^3 as manganese dioxide for 3-6 h/day, up to 10 days).
- A less soluble form of Mn (i.e., insoluble manganese dioxide) was used, whereas more soluble forms (e.g., manganese sulfate, manganese chloride) generally represent greater potential concern (e.g., Dorman et al. 2001, 2004 and Roels et al. 1997 as cited by ATSDR 2012; McGough and Jardine 2017).
- The subacute exposure portion of a monkey study (Dorman et al. 2005) using soluble manganese sulfate, supported by these subacute manganese dioxide studies as well as the results of other studies using soluble Mn (e.g., Saputra et al. 2016, Hamai et al. 2006, McGough and Jardine 2017), is available for derivation of acute ReVs protective of potential adverse health effects due to exposure to more soluble (and less soluble) forms of Mn.

More specifically, the minimal LOAEL of 1.5 mg Mn/m^3 (as manganese sulfate) from the key study of Dorman et al. (2005) provides the point of departure (POD) for derivation of acute 1- and 24-h ReVs.

3.1.1 Key and Supporting Studies

3.1.1.1 Key Animal Study – Dorman et al. (2005)

As part of this subchronic study, subacute inhalation exposure (6 h/day, 5 days/week for 15 exposure days) of young male rhesus monkeys to manganese sulfate ($MnSO_4$) was also performed. Results from the subacute portion of Dorman et al. (2005) serve as the key data for the acute assessment. The subacute portion of the study, which had one exposure group as compared to the subchronic portion that had three exposure groups, and associated results are the primary focus of the discussion here. The control group of monkeys (n = 6) was exposed to air while the exposure group (n = 4 monkeys) was exposed to manganese sulfate at 1.5 mg Mn/m^3 for 6 h/day, 5 days/week and evaluated after 15 days (subacute exposure). Evaluations included measurement of lung Mn concentrations and evaluation of respiratory histologic changes. Tissue Mn concentrations were compared for the exposure and control groups by tests for homogeneity of variance, analysis of variance, followed by Dunnett's multiple comparison. Histopathological findings were statistically evaluated using a Pearson's Chi-Square test.

Exposure to manganese sulfate at 1.5 mg Mn/m^3 for ≥15 exposure days resulted in statistically increased lung Mn concentrations (p<0.05) and some pulmonary pathology including mild subacute bronchiolitis and alveolar duct inflammation (3/4 monkeys, p<0.05) and proliferation of bronchus-associated lymphoid tissue (BALT) (2/4 monkeys, p=0.053). These effects did not occur in any control monkey. Consistent with 15-day exposure results, after a 33-day exposure duration alveolar duct inflammatory changes occurred in 75% (3/4, p<0.05) of the monkeys, and bronchiolitis occurred in 100% (4/4, p<0.05) of the monkeys, affecting a larger percentage of respiratory bronchioles. Again, these lesions did not occur in controls and appeared reversible upon cessation of subchronic Mn exposure. *The TCEQ and National Research Council recommend identifying mild, reversible adverse effects for derivation of inhalation toxicity factors (see Section 3.6.1 of TCEQ 2015).* Manganese sulfate inhalation at 1.5 mg Mn/m^3 for ≥15 exposure days was associated with statistically increased lung Mn concentrations (demonstrating absorption by lung tissue) and mild/minor airway inflammatory changes in the absence of readily observable clinical signs in monkeys (pulmonary function was not further assessed).

Thus, 1.5 mg Mn/m^3 for 15 exposure days is considered by the TCEQ to be a subacute minimal LOAEL for minimal/mild inflammatory airway changes such as mild bronchiolitis, alveolar duct inflammation, and inflammation-induced proliferation of BALT (e.g., found throughout the bronchial tree of smokers but much less frequently in non-smokers, and in humans with panbronchiolitis, chronic hypersensitivity pneumonitis, and other chronic inflammatory airway disease; Richmond et al. 1993). This minimal LOAEL will be applied to exposure durations up to 24 h of exposure since study data demonstrated that the accumulation of Mn in the lung predominated over the 90-h total, 3-week exposure period. That is, after 15 exposure days, lung Mn was statistically significantly increased over controls, demonstrating that toxicokinetic clearance did not occur after each daily 6-h exposure but rather that Mn accumulation in the lung occurred from day to day, and in fact appears to have reached steady state (see Table 2 of Dorman et al. 2005), supporting use of results from this 90-h total exposure for derivation of a 24-h value. Furthermore, use of a minimal LOAEL-to-NOAEL uncertainty factor is justified as opposed to use of the 5-fold lower no-observed-adverse-effect-level (NOAEL of 0.3 mg Mn/m^3) from the subchronic portion of the study due to the very conservative nature of the assessment for derivation of the acute ReVs (i.e., actual exposure duration far exceeding those of interest for the 1- and 24-h ReVs, use of a single day of a 3-week exposure for the 1-h ReV duration adjustment, minimal/mild airway inflammatory changes utilized as endpoints in the absence of observed clinical signs). *Accordingly, the minimal LOAEL of 1.5 mg Mn/m^3 will be used as the POD for both the acute 1- and 24-h ReVs, which is supported by the findings of other studies (see below).*

3.1.1.2 Supporting Studies and Information

3.1.1.2.1 Saputra et al. (2016)

In this study, groups of 12 male Sprague-Dawley rats (250-290 g) were exposed to filtered air (controls) or 39.2 mg Mn/m^3 as manganese chloride ($MnCl_2$) in a nose-only inhalation chamber 4 h/day, 5 days/week, for 3 weeks. Motor coordination was tested on the day after the last exposure using a rotarod device at a fixed speed of 10 rpm for 2 minutes. Following rotarod testing, the rats were euthanized and blood, liver, brain, and lung tissues were collected. Brains were removed and hemisected in the sagittal plane. The right hemisphere was collected for metal analysis, while the left hemisphere was used for protein analysis. Each hemisphere was dissected into four regions: the olfactory bulb, prefrontal cortex, striatum, and cerebellum. Dopamine transporter and dopamine receptor protein expression levels in the striatum region of the brain were determined by Western blot analysis. All left lungs were preserved for histopathology. Right lungs were used for Western blot analysis (e.g., for determining expression of dopamine-related proteins), metal analysis, and non-heme iron (a surrogate for body iron status) analysis. Blood and liver were collected for metal analysis. Wet tissues and blood for metal analysis were weighed and then stored at -70°C until analysis. Serum was used for non-heme iron analysis. Histological examination of the brain, lung, and nasal cavity were conducted. The overall average mass concentration and mass median aerodynamic diameter (MMAD) of the $MnCl_2$ aerosol were 39.2 ± 2.8 mg Mn/m^3 and 1.2 μm, respectively.

Body weight, hematocrit, brain weights, and lung weights were not significantly different in the rats in the exposure group compared to those in the control group. While the liver weight decreased (9%), the relative liver to body weight did not differ significantly from that in the control group. These results indicate that there were no physiological alterations as a result of a short-term Mn exposure. At a rotarod speed of 10 rpm, there were no significant differences in the time on the bar before the first fall or the number of falls during the two-minute test observed in the exposed rats, as compared with controls. Thus, short-term exposure to Mn aerosol did not cause motor impairment in exposed rats as evaluated. The Mn-exposed group had significantly higher Mn levels in the lung, blood, olfactory bulb, prefrontal cortex, striatum, and cerebellum compared with the control group. A Mn concentration gradient was observed from the olfactory bulb to the striatum, supporting that Mn is transported via the olfactory pathway. These results suggest that the short-term Mn inhalation in this study increased Mn levels in the brain and lung, the two primary sites of Mn deposition after inhalation exposure, but not in the liver (the site of Mn storage). Short-term exposure to Mn by inhalation did not cause any apparent disruption of body iron homeostasis. Since Mn exposure is known to be related to disruption of dopamine pathway, expressions of dopamine-related proteins were determined by Western blot analysis. Mn exposure reduced dopamine transporter levels, while there were no significant differences in the levels of striatal dopamine receptor. *Finally, while histological examination of the brain did not reveal histopathological damage or neuronal degeneration, the authors reported that Mn deposition in the lung altered lung histopathology at the respiratory bronchioles (pulmonary region) and caused mild/minor lung injury but no clinical signs of injury in other tissues.* Minimal induction of inflammatory cell infiltration was reported (see Figure 6 of the study).

In accordance with the discussion above, the study reported that inhalation exposure to 39.2 mg Mn/m^3 Mn for 3 weeks induced mild lung injury and modulation of dopamine transporter expression in the brain, without altering motor activity. Thus, for this study, 39.2 mg Mn/m^3 is the minimal LOAEL for the mild lung injury reported in rats exposed 4 h/day, 5 days/week, for 3 weeks. *This subacute rat LOAEL, combined with the concentration (13.1 mg Mn/m^3) reported to induce crackling/gasping respiration in some rats during 3-week exposure in the range finding study for McGough and Jardine (2017) (discussed below), provides considerable support for use of the subacute monkey LOAEL from the key study (e.g., much more serious adverse effects are reported to be associated with subacute exposure to 13.1 mg Mn/m^3).*

3.1.1.2.2 McGough and Jardine (2017)

For the range finding rat study (details not provided) of the McGough and Jardine (2017) reproductive study (discussed more in Section 3.1.1.3), *exposure to 30 mg/m^3 (as $MnCl_2$, equating to 13.1 mg Mn/m^3) was ceased at 3 weeks due to adverse clinical signs of crackling/gasping respiration that resulted in the premature sacrifice of 15% (3/20) of the animals. Necropsy findings included discolored lungs and a froth-filled trachea*. In the main study, the authors did not consider the respiratory effects induced by $MnCl_2$ to be a unique toxicological effect of $MnCl_2$ but more an effect from the slower lung clearance of Mn^{2+} and the irritating effect from the Cl_2. Regardless of the extent to which the irritating effect of Cl_2 may have contributed to the respiratory effects of $MnCl_2$ apart from Mn^{2+}, the fact remains that Mn in Texas and elsewhere may be emitted as $MnCl_2$. For example, in 2009 Texas had approximately 200 facilities that used, processed, or produced Mn compounds, and $MnCl_2$ is used as a precursor for other Mn compounds, as a catalyst in the chlorination of organic compounds, in animal feed to supply essential trace minerals, and in dry-cell batteries (ATSDR 2012). Another Mn compound, methylcyclopentadienyl manganese tricarbonyl (MMT), is an octane enhancer allowed in US gasoline that results in manganese emissions primarily in the phosphate- and sulfate-forms. These forms, like $MnCl_2$, are more soluble forms that are generally of greater potential concern, with smaller amounts of manganese oxides (Dorman et al. 2005). *Therefore, the database considered for the acute assessment should include information on the respiratory effects of soluble forms such as $MnSO_4$ and $MnCl_2$ so that the resulting toxicity factors may serve as appropriate if not reasonably conservative comparison values depending upon the form of Mn emitted, and can be expected to be adequately protective against the potential short-term, adverse health effects of Mn (i.e., regardless of the inorganic form emitted, except for permanganates which are not addressed by this DSD).*

Reported observation of the more severe clinical signs of crackling/gasping respiration, discolored lungs, and a froth-filled trachea in some rats during 3-week exposure to 30 mg $MnCl_2$/m^3 (13.1 mg Mn/m^3) in the range finding study for McGough and Jardine (2017) provides considerable support for use of the lower non-human primate LOAEL from the key study (1.5 mg Mn/m^3 as $MnSO_4$) for less serious effects in monkeys.

3.1.1.2.3 Other Supporting Information

The sensitivity of the respiratory system as a target for Mn compounds is also supported more generally by the results of other studies with subacute exposure to less soluble manganese dioxide (e.g., 10-day rat LOAEL of 43 mg Mn/m^3 for pneumonitis and increased lung weight in Shiotsuka 1984; 4-day mouse LOAEL of 69 mg Mn/m^3 for increased pneumonia in Maigetter et al. 1976). The Mn pneumonitis and increased pneumonia reported in some animal studies (e.g., Shiotsuka 1984, Maigetter et al. 1976) is consistent with reports of these same effects in Mn-exposed workers at least as early as 1921 (Lloyd Davies and Harding 1949). *Thus, additional animal studies support respiratory tract effects as critical adverse effects due to subacute exposure, irrespective of solubility (i.e., manganese sulfate versus manganese dioxide).*

In regard to effects on the transcription of genes at low exposure concentrations that cannot be considered biologically adverse, Hamai et al. (2006) examined the transcriptional patterns of genes related to oxidative stress or inflammation in the brain rats of exposed to inhaled Mn during either gestation or early adulthood. Although not considered biologically adverse, these changes are discussed here since the brain/neurological effects of Mn are a primary concern and the results of this study help put results of the acute assessment into a broader context. In Hamai et al. (2006), there were three groups of rats (3-5 animals per group) exposed to 0 or 0.71 mg Mn/m^3 (as manganese sulfate):

- For the prenatally-exposed group, female pregnant Sprague-Dawley rats were exposed 2 h/day on gestation days (GDs) 9 and 10 (4 h of prenatal exposure total);
- The adult group was exposed at 6 weeks after birth, 2 h/day for 10 consecutive days (20 h of adult exposure total);
- For the prenatal + adulthood exposure group, animals were exposed 2 h/day on GDs 9 and 10 and again for 10 days at 6 weeks of age (24 h of exposure total).

Brain levels of mRNA were measured for gene products related to oxidative stress or inflammation. Gestational exposure was associated with statistically significant ($p<0.05$) decreased mRNA for amyloid precursor protein (APP; a redox-sensitive neurotrophic factor), cyclooxygenase-2 (COX-2; a redox-sensitive neurotrophic factor), neuronal nitric oxide synthetase (nNOS; a redox-sensitive neurotrophic factor), and glial fibrillary acidic protein (GFAP; an inflammation-related, redox-sensitive neurotrophic factor). Adult exposure was associated with greater statistically significant transcriptional decreases for the same gene products as well as transformation growth factor beta (TGF-β; a redox-sensitive cytokine) (ATSDR 2012, Hamai et al. 2006). In other words, the expression of genes encoding for proteins critical to an inflammatory response and/or possessing pro-oxidant properties, including TGF-β and nNOS, were slightly depressed by prenatal exposure, whereas inhalation exposure to Mn during adulthood more markedly down-regulated their transcription. However, when exposures occurred during gestation, the extent of altered gene expression induced by subsequent exposure to Mn in adulthood was reduced (e.g., prenatal + adulthood exposure

produced smaller but still statistically significant ($p<0.05$) decreases in COX-2, nNOS, and TGF-β mRNA than adulthood only exposure, whereas prenatal exposure produced decreases similar to prenatal + adulthood exposure). This suggests that prior prenatal exposure to Mn may have attenuated the effects of inhalation exposure to Mn in adulthood, during which the expression of inflammation-related genes were suppressed. Whole brain levels of Mn were higher in exposed animals, but did not reach statistical significance (Hamai et al. 2006).

While excess levels of immune components and neurotrophic factors APP, COX-2, GFAP, nNOS, and TGF-β can have potential adverse effects, in this case Mn inhalation exposure induced down regulation in the brain. These changes cannot be defined as biologically adverse (Hamai et al. 2006, ATSDR 2012), and as such are not considered critical effects (TCEQ 2015). Consequently, 0.71 mg Mn/m^3 is considered a LOEL and not a candidate POD for acute ReV derivation in this case. *However, for context and support, the LOEL of 0.71 mg Mn/m^3 will be used for margin of exposure (MOE) analysis for both the acute 1- and 24-h ReVs based on Dorman et al. (2005).* In doing so, the LOEL is considered to apply to exposure durations up to 24 h since the half-life of Mn in the brains of rats and humans is long (e.g., between 51-74 days; DFG 2015) relative to the study exposure durations that produced the effects observed (e.g., a relatively long half-life in the brain suggests, for example, that the accumulation of Mn predominates over a 10-day/20-h total exposure period).

3.1.1.3 Consideration of Developmental/Reproductive Effects

Summary information of available data on potential Mn-induced reproductive effects was taken from ATSDR (2012). Men who are exposed to Mn dust in workplace air report decreased libido and impotency (Emara et al. 1971, Mena et al. 1967, Rodier 1955), and may suffer from sexual dysfunction (Jiang et al. 1996) and decreased sperm and semen quality (Wu et al. 1996). In addition, studies in animals indicate that Mn can cause damage to the testes such as severe degenerative changes in the seminiferous tubules that lead to sterility 4-8 months following intratracheal instillation (Chandra et al. 1973, Seth et al. 1973). While the Jiang et al. (1996) study suggests testicular damage in occupationally exposed men, future epidemiological studies to more fully evaluate reproductive function may provide definitive exposure-response data on reproductive function (e.g., impotence, libido, number of children). Information on adverse reproductive effects in women is not available. Data from studies in female animals indicate that Mn can cause post-implantation loss when administered through both oral and subcutaneous exposure routes in female mice and rats (Colomina et al. 1996, Sánchez et al. 1993, Szakmáry et al. 1995, Treinen et al. 1995).

In regard to more recent studies, McGough and Jardine (2017) investigated potential Mn-induced effects on the reproductive systems of Sprague-Dawley rats. This study involved both subacute and chronic exposure regimens, both of which will be discussed here for convenience (parsing subacute and chronic results would also result in a less complete toxicological picture), although relevant subacute exposure results will ultimately be the focus of this section. In this

OECD Guideline 416 and USEPA Guideline OPPTS 870.3800 compliant study, male and female rats were exposed to $MnCl_2$ via nose-only inhalation at target concentrations of 0 (controls), 5, 10, and 20 µg/L (equivalent to mg/m^3) for 6 h/day, 7 days/week over 10 weeks (F0; 28 per sex) and over 11 weeks (F1; 24-26 per sex) (i.e., subchronically exposed) prior to mating, and then throughout mating, gestation, and lactation until termination of the F0 and F1 generations after the F1 and F2 generations, respectively, had reached day 21 of lactation. However, exposure was only 1 h/day for lactation days 1-2 and 2 h/day for lactation days 3-4, with exposure 6 h/day for lactation days 5-20. Actual concentrations were 0, 6, 15, and 25 mg/m^3 for the F0 generation exposure groups and 0, 4, 10, and 17 mg/m^3 for the F1 generation. As mentioned in Section 3.1.1.2.2, *notably in the 9-week range finding study (details not provided), exposure was reportedly stopped after only 3 weeks (a subacute exposure duration) for a 30 mg/m^3 exposure group (10 animals per sex) due to adverse clinical signs of crackling/gasping respiration that resulted in the premature sacrifice of 3/20 animals (e.g., necropsy findings included discolored lungs, froth-filled trachea)*. In the main study, animals were monitored for clinical signs of toxicity and for effects on body weight, food consumption, effects on estrous cycles, mating performance, pregnancy performance, difficulty or prolongation of parturition, and for deficiencies in maternal care. The offspring were monitored for survival and growth up to weaning. In addition, the following endpoints were evaluated: gross necropsy findings, organ weights, histopathology evaluation, qualitative examination of testes and examination of the ovaries and sperm. Blood samples were taken from all adult animals for bioanalytical of manganese analysis prior to dosing, prior to mating, and prior to weaning/necropsy (see the study for more details).

There were no deaths related to treatment. Respiratory symptoms were observed in F0 animals in the 15 and 25 mg/m^3 dose groups. Wheezing combined with other clinical signs (i.e., unkempt coat, walking on tip toes, rolling gait, weight loss) exhibited by the one F0 female in the 15 mg/m^3 dose group were not attributed by study authors to the exposure as no similar findings were noted in other animals of this exposure group or at 25 mg/m^3. *Wheezing respiration in two F0 males of the 25 mg/m^3 dose group was attributed to exposure. In regard to other respiratory effects, for all treated F0 females there was a statistically significant increase in absolute lung weights, and these increases were still statistically significant following covariance analysis with body weight ($p<0.01$ at 6 mg/m^3, $p<0.001$ at 15 and 25 mg/m^3).* However, percent increases in organ weight or organ-to-body weight could not be calculated by the TCEQ as the study did not report the weights. Histological findings related to treatment were confined to the respiratory tract as follows:

<u>F0 Generation</u>

- Larynx - There was a broadly dose-related minimal to moderate squamous metaplasia with minimal to moderate submucosal inflammation; minimal to marked ulceration of the

laryngeal epithelium was associated with the squamous metaplasia in several animals from all exposed groups (6, 15, and 25 mg/m^3).

- Lungs - The principal exposure-related change was seen in centroacinar regions where there was minimal or mild inflammation and focal or diffuse minimal or mild broncho-alveolar hyperplasia. Also, minimal or mild goblet cell hyperplasia in the bronchial or bronchiolar epithelium was present in animals exposed to 25 mg/m^3 together with occasional incidences of degeneration and/or squamous metaplasia of the bronchiolar epithelium. There was minimal inflammatory findings (inflammatory cell foci and perivascular inflammatory cell infiltration) were also present with a greater incidence in exposed animals.
- Nose - Minimal or mild goblet cell hyperplasia and minimal to moderate eosinophilic globules in the olfactory epithelium were observed in all the male treated groups and in females exposed to 15 or 25 mg/m^3. At all dose levels (6, 15, and 25 mg/m^3) there was a greater incidence of minimal or mild submucosal inflammatory cell infiltration compared to controls. In males, inflammation of the nasolacrimal duct and squamous metaplasia of the ductal epithelium was seen in most animals exposed to 15 or 25 mg/m^3. In addition to these changes, incidences of minimal or mild focal degeneration of the olfactory, respiratory or transitional epithelia, minimal or mild atrophy of the olfactory epithelium, ulceration and focal squamous metaplasia were observed, mainly in animals exposed to 15 or 25 mg/m^3, but occasionally in animals at 6 mg/m^3.
- Pharynx - Minimal goblet cell hyperplasia was observed in the pharynx of most males exposed to 25 mg/m^3 and there were occasional incidences of minimal or mild focal epithelial degeneration, focal inflammation and focal squamous metaplasia in males exposed at 15 or 25 mg/m^3.
- Trachea - Minimal or mild focal squamous metaplasia and inflammation at the carina and minimal or mild focal epithelial degeneration at sites other than the carina were observed at all dose levels (6, 15, and 25 mg/m^3).

<u>F1 Generation</u>

- Nose - Squamous metaplasia in the nasal cavity was observed mainly in the nasolacrimal duct and to a lesser extent in the transitional and respiratory epithelia (doses not specified).
- Trachea - Findings such as epithelial degeneration, squamous metaplasia and submucosal inflammation were observed predominantly in the carina (doses not specified).

Body weight and food consumption were affected at the high dose in both generations. For example, there was a 29% decrease in weight gain over days 0-21 in F0 males at 25 mg/m^3, although weight gain mostly recovered and was lower but comparable from day 21 and food consumption was reduced in these males throughout most of the study. In regard to other treatment-related organ weight effects, *there was a statistically significant increase in kidney*

weights in F1 females at 10 and 17 mg/m^3 following covariance analysis with body weight (p<0.05 at 10 mg/m^3, p<0.001 at 17 mg/m^3).

There were no treatment-related effects on the estrous cycles, mating performance, sexual maturity, fertility or duration of gestation or litter size, the sperm motility, count of morphology (sperm), or the ovary follicle scoring in either generation. The no-observed-effect-level (NOEL) for reproductive performance was considered to be the target concentration of 20 mg/m^3. *Based on these findings, study authors concluded that manganese chloride could not be considered a reproductive toxicant under conditions of the study, and therefore, soluble and insoluble forms of inorganic manganese compounds by extrapolation cannot be considered as reproductive toxicants.*

As summarized by the study authors, apart from the respiratory tract (i.e., effects were seen in the nasal cavity, larynx, lung and trachea [including carina], and pharynx in the F0 and F1 generations), there were no systemic toxic effects due to $MnCl_2$ up to the target concentration of 20 mg/m^3. Respiratory tract effects were not considered by McGough and Jardine to be a unique toxicological effect from $MnCl_2$ but more an effect from the slower lung clearance of Mn^{2+} and the irritating effect from the Cl_2 (i.e., "free chloride ions aggressive to the lung lining causing local reactions and even lesions"). Thus, per the study's authors, the parental NOAEL was considered to be the target level of 20 mg/m^3 (25 mg/m^3 analytical) and the NOEL for reproductive performance was considered to be the target dose level of 20 mg/m^3. As concentrations are discussed in the study as $MnCl_2$, the TCEQ notes that the Mn concentration corresponding to the cited chronic NOAEL/NOEL target concentration of 20 mg $MnCl_2$/m^3 would be 8.7 mg Mn/m^3 (i.e., MW Mn/MW $MnCl_2$ = 54.94/125.84 = 0.4366 $\times$ 20 mg $MnCl_2$/m^3 = 8.73 mg Mn/m^3). However, regardless of the extent to which the irritating effect of Cl_2 may have contributed to the respiratory effects of chronic $MnCl_2$ exposure apart from Mn^{2+}, the fact remains that Mn in Texas and elsewhere may be emitted as $MnCl_2$ with the same potential to induce effects.

Furthermore, the TCEQ notes:

- Statistically significant increases in lung weight following covariance analysis with body weight for *all* treated F0 females (p<0.01 at 6 mg/m^3, p<0.001 at 15 and 25 mg/m^3); and
- Statistically significant increases in kidney weight in F1 females at 10 and 17 mg/m^3 following covariance analysis with body weight (p<0.05 at 10 mg/m^3, p<0.001 at 17 mg/m^3).

Consideration of study results suggests that a *chronic* LOAEL based on this study could be as low as 6 mg $MnCl_2$/m^3 (e.g., 2.6 mg Mn/m^3 based on lung weight and/or other respiratory effects) or 10 mg $MnCl_2$/m^3 (4.4 mg Mn/m^3 based on kidney weight). These results are considered further in the chronic section (Section 4.1.1.2).

Finally, in regard to the relevance of McGough and Jardine (2017) for derivation of acute ReVs, the TCEQ notes that exposure to 30 mg $MnCl_2/m^3$ (13.1 mg Mn/m^3) was stopped at 3 weeks (subacute exposure) during the range finding study due to adverse clinical signs of crackling/gasping respiration in some animals (also, necropsy findings included discolored lungs, froth-filled trachea). *These reported results for more severe subacute effects in rats at 13.1 mg Mn/m^3 support use of the lower subacute monkey LOAEL of 1.5 mg Mn/m^3 for more minimal/mild respiratory effects from the 3-week portion of the key study (Dorman et al. 2005).*

Developmental studies on the potential effects of the inhalation or ingestion of Mn compounds are very limited, particularly in humans, although the limited oral human studies available support the hypothesis that Mn exposure may be detrimental to childhood neurodevelopment (ATSDR 2012). In regard to laboratory animals, see the discussion of the Hamai et al. (2006) rat study (acute/subacute exposure) in Section 3.1.1.2.3. Additionally, Lown et al. (1984) evaluated the developmental effects of inhaled Mn. The study, which had many complications, involved exposing dams and non-pregnant female mice to either filtered air or Mn at an average concentration of 61 mg Mn/m^3 (as manganese dioxide), 7 h/day, 5 days/week, for 16 weeks prior to conception (ATSDR 2012). The authors then exposed the mice to either air or Mn post-conception, irrespective of pre-conception exposure. Once delivered, six pups (three of each sex) were distributed to foster mothers and then nursed in the absence of Mn exposure. The pups were then evaluated on postpartum day 7 for weight gain and gross locomotor activity and on day 45 for different behavioral parameters and learning performance. *The authors observed that pups raised by foster mothers that had been exposed to Mn pre-conception and filtered air post-conception had reduced weights compared to pups raised by foster mothers exposed only to filtered air*. The activity data indicated that there were no observable differences in activity between pups who had been exposed to Mn *in utero* and those that had not (ATSDR 2012). This potential inhalation LOAEL/POD (61 mg Mn/m^3) for reduced pup body weight, however, is appreciably higher than the minimal LOAEL (1.5 mg Mn/m^3) for minimal/mild respiratory effects in non-human primates used by the TCEQ as the POD for derivation of acute ReVs.

In regard to oral studies in laboratory animals, standard developmental toxicity studies have not found distinct effects on fetal survival, gross fetal malformations, or skeletal or visceral malformations or alterations (ATSDR 2012). For example, acute administration of $MnCl_2$ by gavage to pregnant rats at a dose of 22 mg Mn/kg-day on GDs 6-17 resulted in no adverse fetal developmental effects, measured as weight gain, gross malformations, or skeletal malformations (Grant et al. 1997). In another study, Szakmáry et al. (1995) reported on the developmental toxicity of Mn in the rabbit and Sprague-Dawley rat. The metal, as $MnCl_2$, was administered by gavage during the whole period of gestation in the rat, and during organogenesis (day 6-20) in the rabbit at concentrations of 0, 11, 22, and 33 mg Mn/kg-day. In the rabbit, Mn treatments did not result in decreases in fetal weights, skeletal retardation, or extra ribs, or in an increase in fetuses afflicted with major anomalies. In the rat, while the

middle dose (22 mg Mn/kg-day) resulted in increased relative organ weights (i.e., liver, thymus, brain), the highest dose (33 mg Mn/kg-day) resulted in post-implantation loss (a reproductive effect) and retardation of development of the skeleton and internal organs. In addition, Mn at the highest dose caused a significant increase in external malformations, such as clubfoot. However, when pups from dams treated at the same dose were allowed to grow for 100 days after birth, no external malformations were observed, indicating that these effects were self-corrected. No significant differences were found in any of the groups concerning the development of the ears, teeth, eyes, forward motion, clinging ability, body posture correction reflex, or negative geotaxis reflex (ATSDR 2012). Other oral developmental rat studies involving postnatal exposure have shown developmental effects at lower LOAELs (e.g., increased pulse-initiated acoustic startle response at 11 mg Mn/kg-day in Dorman et al. 2000; increased spontaneous motor activity and ≈ 20% decrease in body weight at 22 mg Mn/kg-day in Brenneman et al. 1999), and some studies involving gestational and postnatal exposure combined (to some extent) provide LOAELs as low as 4.4-8 mg/kg-day (e.g., significant ($p<0.05$), dose-related gliosis in the brains of rat pups in Lazrishvili et al. 2009; hematological changes indicative of iron deficiency in dams and pups and increased levels of the inhibitory neurotransmitter GABA in pup brains in Garcia et al. 2006). These oral neurological LOAELs are similar to some observed in adult animals (e.g., in Shukakidze et al. 2003, decreased acquisition of an avoidance reaction in rats due to 1-day exposure to 13.9 mg Mn/kg-day and severely impaired cognitive performance in a maze test following subacute/30-day exposure to 5.6 mg Mn/kg-day), and are part of the weight-of-evidence from oral neurodevelopmental animal studies suggesting that excess Mn exposure during development can lead to alterations in brain chemistry and behavioral development (ATSDR 2012). See Table 3-2 of ATSDR (2012) for additional developmental studies and information. As a simple example assuming similar absorption across routes, the air concentration corresponding to an adult rat oral dose LOAEL of 4.4 mg Mn/kg-day is approximately 5 mg Mn/m^3 (i.e., 4.4 mg Mn/kg-day $\times$ 0.25 kg = 1.1 mg Mn/day / 0.22 m^3/day ≈ 5 mg Mn/m^3).

These results highlight the importance of adequate developmental studies by the inhalation route (as well as the toxicokinetic accuracy of any route-to-route extrapolations), which are lacking. Additionally, although several (mainly oral) developmental studies have been performed in animals, they are mainly limited to rodent species and have measured limited developmental endpoints. Moreover, the fact that non-human primates are very sensitive to the neurological effects of Mn is critically important, especially considering that rodent models do not exhibit the same neurological symptoms as humans and monkeys despite high doses through inhalation, oral, and intravenous routes (ATSDR 2012). *Thus, especially considering this apparent difference in susceptibility in humans/non-human primates versus rodents, the rodent results discussed above do not assuage potential developmental neurological concerns for humans.* Study evaluations of appropriate and sensitive developmental neurological endpoints by the inhalation (and oral) route are needed as Mn-induced neurological effects are a primary concern based on the existing database (e.g., see Section 3.12.2 of ATSDR 2012).

3.1.2 Health-Based Acute 1-h ReV and ESL

3.1.2.1 Adjustments to the POD

3.1.2.1.1 Duration Adjustments

As mentioned in Section 3.1.1.1, the minimal LOAEL of 1.5 mg Mn/m^3 will be used as the POD for both the acute 1- and 24-h ReVs (Dorman et al. 2005). Quite conservatively for the acute 1-h ReV, the 6-h duration LOAEL/POD (C_1) from a single day of exposure was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity (TCEQ 2015):

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(1.5 \text{ mg } Mn/m^3)^3 \times (6 \text{ h}/1 \text{ h})]^{1/3}$$
$$= 2.72 \text{ mg } Mn/m^3 = POD_{ADJ}$$

Thus, the duration-adjusted POD (POD_{ADJ}) for derivation of the 1-h ReV is 2.72 mg Mn/m^3.

3.1.2.1.2 Adjustment from Animal-to-Human Exposure

Since Dorman et al. (2005) indicate that the predicted pulmonary deposition efficiency of a particle size similar to that used in the study (MMAD of 1.72-2.12 µm) is approximately 35% for both rhesus monkeys and humans, a regional deposited dose ratio (RDDR) of 1 was used due to the similar lung anatomy.

Thus, to derive the POD_{HEC} value, the POD_{ADJ} for the 1-h ReV was multiplied by the RDDR of 1:

$$\text{1-h ReV } POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 2.72 \text{ mg } Mn/m^3 \times 1$$
$$= 2.72 \text{ mg } Mn/m^3$$

This POD_{HEC} value is used below to derive the acute 1-h ReV in Table 3.

To evaluate MOE, a 1-h LOEL-based POD_{HEC} value was also calculated based on Hamai et al. (2006). Duration adjustment of the study POD (710 µg Mn/m^3) resulted in a 1-h POD_{ADJ} value of 894.5 µg Mn/m^3. Using the Multiple Pass Particle Dosimetry (MPPD) Model (version 2.11) (CIIT 2004) with the MMAD (0.55 µm) and σ_g (1.5) provided by Hamai et al. (2006) resulted in a RDDR of 4.25 and 1-h POD_{HEC} value of 3,802 µg Mn/m^3 (calculations not shown). This 1-h POD_{HEC} value, which represents a study NOAEL as the observed changes cannot be defined as biologically adverse, will be used to calculate a MOE based on the 1-h ReV.

3.1.2.2 Uncertainty Factors

The default approach for noncarcinogenic effects is to determine a POD and apply appropriate uncertainty factors (UFs) to derive ReVs (i.e., assume a threshold mode of action; TCEQ 2015) and review of available mode of action (MOA) and other information (e.g., Mn is an essential element) did not indicate that an alternate approach would be more scientifically defensible (e.g., toxicologically predictive). The same UFs were applied to the POD_{HEC} values for both the acute 1- and 24-h ReVs. While the total *potential* UF is 360 (i.e., UF_L of 2 $\times$ UF_H of 10 $\times$ UF_A of 3 $\times$ UF_D of 6 = 360; see below), the total *maximum* acute UF of 300 was applied, consistent with TCEQ guidelines (TCEQ 2015).

- A reduced UF_L of 2 was used for extrapolation from a LOAEL to a NOAEL since the observed pulmonary pathology was characterized as mild/minor airway inflammatory changes in the absence of observable clinical signs;
- A full UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions);
- A UF_A of 3 was used to account for potential toxicodynamic differences between rhesus monkeys and humans; and
- A UF_D of 6 was used for limitations/uncertainties in the acute/subacute database including the lack of toxicological data on: (1) humans exposed acutely (or subacutely) to either less soluble forms of Mn or the more soluble forms of greater potential concern for the general population; and (2) whether acute/subacute exposure to inhaled Mn has a significant potential for adverse effects on numerous endpoints including developmental neurological effects, and if so (as suggested by the oral developmental database, as well as neurological/ neurobehavioral changes being the critical effects based on the intermediate- and chronic-duration databases), what exposure concentrations/durations induce them (ATSDR 2012). That is, additional studies involving neurobehavioral effects following gestational and postnatal exposure to airborne Mn are necessary. The addition of developmental neurotoxicology studies using a functional observational battery design and a wide range of well-established measures would result in a more complete inhalation (and oral) database, particularly if non-human primates are used considering that rodents may be a less-than-desirable model for neurological effects in humans (i.e., rodent models do not appear to be as susceptible to Mn-induced neurotoxicity as humans and monkeys, somewhat diminishing the relevance of chronic Mn inhalation exposure rodent neurological results in regard to their ability to help identify the most sensitive Mn effects that may occur in humans) (see Section 3.12.2 of ATSDR 2012). Additionally, while some acute/subacute studies demonstrate either free-standing NOAELs or LOAELs/LOELs, they do not demonstrate these values in the context of studies adequate to fully characterize dose-response for the endpoints studied. These database limitations result in a low confidence in the acute/subacute database overall (TCEQ 2015), consistent with ATSDR (2012) not deriving an acute duration minimal risk level (MRL) (inhalation or oral).

Table 5. Derivation of the Acute 1-h ReV and ^{acute}ESL

Parameter	Summary
Key Study	Dorman et al. (2005)
Study Population	Rhesus monkeys
Study Quality Confidence Level	Medium-high
Exposure Method	Inhalation
Critical Effects	Minimal/mild inflammatory airway changes (i.e., mild bronchiolitis, alveolar duct inflammation, proliferation of BALT)
Exposure Duration	6 h/day, 5 days/week, for 3 weeks (90 h total exposure)
POD (minimal LOAEL)	1.5 mg Mn/m^3 (6 h)
Extrapolation to 1-h	2.72 mg Mn/m^3 using Haber's Rule as modified by ten Berge (1986) with n=3
POD_{HEC}	2.72 mg Mn/m^3 (RDDR = 1)
Total potential uncertainty factor (UF)	360
LOAEL to NOAEL UF	2
Intraspecies UF	10
Interspecies UF	3
Database UF *Database Quality*	6 Low
Total *maximum* acute UF	300
1-h acute ReV (HQ = 1)	**9.1 µg Mn/m^3**
1-h ^{acute}ESL (HQ = 0.3)	**2.7 µg Mn/m^3**

3.1.3 Health-Based Acute 24-h ReV

3.1.3.1 Adjustments to the POD

3.1.3.1.1 Duration Adjustment

For the 24-h ReV, the LOAEL/POD of 1.5 mg Mn/m^3 was used as the 24-h POD_{ADJ} since the total exposure duration was considerably longer (i.e., 90 h) and lung tissue data from the study indicates that the accumulation of Mn in the lung predominated over the 3-week exposure period. Thus, the POD_{ADJ} for derivation of the 24-h ReV is 1.5 mg Mn/m^3.

3.1.3.1.2 Adjustment from Animal-to-Human Exposure

Since Dorman et al. (2005) indicate that the predicted pulmonary deposition efficiency of a particle size similar to that used in the study (MMAD of 1.72-2.12 μm) is approximately 35% for both rhesus monkeys and humans, a RDDR of 1 was used.

Thus, to derive a POD_{HEC} value, the POD_{ADJ} for the 24-h ReV was multiplied by the RDDR of 1:

$$\begin{aligned} \text{24-h ReV } POD_{HEC} &= POD_{ADJ} \times RDDR \\ &= 1.5 \text{ mg Mn/m}^3 \times 1 \\ &= 1.5 \text{ mg Mn/m}^3 \end{aligned}$$

To evaluate MOE, a 24-h LOEL-based POD_{HEC} value was also calculated based on Hamai et al. (2006). Duration adjustment of the study POD (710 μg Mn/m^3) resulted in a 24-h POD_{ADJ} value of 591.7 μg Mn/m^3. Using the MPPD Model (CIIT 2004) with the MMAD (0.55 μm) and σ_g (1.5) provided by Hamai et al. (2006) resulted in a RDDR of 4.25 and 24-h POD_{HEC} value of 2,515 μg Mn/m^3 (calculations not shown). This 24-h POD_{HEC} value, which represents a study NOAEL as the observed changes cannot be defined as biologically adverse, will be used to calculate a MOE based on the 24-h ReV.

3.1.3.2 UFs

As mentioned previously, the same UFs were applied to the POD_{HEC} value for the acute 24-h ReV as for the 1-h ReV. While the total *potential* UF is 360 (i.e., UF_L of 2 × UF_H of 10 × UF_A of 3 × UF_D of 6 = 360; see below), the total *maximum* acute UF of 300 was applied, consistent with TCEQ guidelines (TCEQ 2015).

- A reduced UF_L of 2 was used for extrapolation from a LOAEL to a NOAEL since the observed pulmonary pathology was characterized as mild/minor airway inflammatory changes in the absence of observable clinical signs;
- A full UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions);
- A UF_A of 3 was used to account for potential toxicodynamic differences between rhesus monkeys and humans; and
- A UF_D of 6 was used for limitations and uncertainties in the acute/subacute database including the lack of toxicological data on: (1) humans exposed acutely (or subacutely) to either less soluble forms of Mn or the more soluble forms of greater potential concern for the general population; and (2) whether acute/subacute exposure to inhaled Mn has a significant potential for adverse effects on numerous endpoints including developmental neurological effects, and if so (as suggested by the oral developmental database, as well as neurological/neurobehavioral changes being the critical effects based on the intermediate- and chronic-duration databases), what exposure concentrations/durations induce them (ATSDR 2012). That is, additional studies involving neurobehavioral effects following

gestational and postnatal exposure to airborne Mn are necessary. The addition of developmental neurotoxicology studies using a functional observational battery design and a wide range of well-established measures would result in a more complete inhalation (and oral) database, particularly if non-human primates are used considering that rodents may be a less-than-desirable model for neurological effects in humans (i.e., rodent models do not appear to be as susceptible to Mn-induced neurotoxicity as humans and monkeys, somewhat diminishing the relevance of chronic Mn inhalation exposure rodent neurological results in regard to their ability to help identify the most sensitive Mn effects that may occur in humans) (see Section 3.12.2 of ATSDR 2012). Additionally, while some acute/subacute studies demonstrate either free-standing NOAELs or LOAELs/LOELs, they do not demonstrate these values in the context of studies adequate to fully characterize dose-response for the endpoints studied. These database limitations result in a low confidence in the acute/subacute database overall (TCEQ 2015), consistent with ATSDR (2012) not deriving an acute duration minimal risk level (MRL) (inhalation or oral).

Table 6. Derivation of the Acute 24-h ReV

Parameter	Summary
Key Study	Dorman et al. (2005)
Study Population	Rhesus monkeys
Study Quality Confidence Level	Medium-high
Exposure Method	Inhalation
Critical Effects	Minimal/mild inflammatory airway changes (i.e., mild bronchiolitis, alveolar duct inflammation, proliferation of BALT)
Exposure Duration	6 h/day, 5 days/week, for 3 weeks (90 h total exposure)
POD (minimal LOAEL)	1.5 mg Mn/m^3 (6 h)
POD_{HEC}	1.5 mg Mn/m^3 (RDDR = 1)
Total *potential* UF	360
LOAEL to NOAEL UF	2
Intraspecies UF	10
Interspecies UF	3
Database UF *Database Quality*	6 *Low*
Total *maximum* acute UF	300
24-h acute ReV (HQ = 1)	**5.0 µg Mn/m^3**

The 1- and 24-h ReVs provide MOEs of approximately 400-500 compared to the respective 1- and 24-h NOAEL POD_{HEC} values (3,802 and 2,515 µg Mn/m^3) based on Hamai et al. (2006), wherein no adverse effects on the brains of rats were demonstrated.

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

An $^{acute}ESL_{odor}$ value is not applicable to Mn and inorganic Mn compounds due to a lack of odor potential.

3.2.2 Vegetation Effects

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne Mn.

3.3 Acute Values for Air Permitting and Air Monitoring Evaluations

This acute evaluation resulted in the derivation of the following acute values for Mn and inorganic compounds:

- 1-h ReV = 9.1 µg Mn/m^3
- 1-h ^{acute}ESL = 2.7 µg Mn/m^3
- 24-h ReV = 5.0 µg Mn/m^3

The 1-h ^{acute}ESL for air permit evaluations is 2.7 µg Mn/m^3 (Table 2). The 24-h ReV of 5.0 µg Mn/m^3 will be used for the evaluation of air monitoring data, although the 1-h ReV may be used as appropriate in the event air sampling is conducted over a comparable duration (Table 1).

3.4 Subacute Inhalation Observed Adverse Effect Level

Risk assessors and the general public are interested in information on air concentrations where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies may identify a lower POD for this purpose. Regarding critical effects due to acute Mn exposure, the Rhesus monkey study of Dorman et al. (2005) provides a 6-h/day, 5 days/week, 3-week minimal LOAEL of 1,500 µg Mn/m^3 for mild inflammation airway changes (e.g., mild bronchitis). Consistent with guidelines, no duration adjustment was made for the subacute inhalation observed adverse effect level (TCEQ 2015). Thus, since the RDDR equals 1, the $LOAEL_{HEC}$ of 1,500 µg Mn/m^3 will serve as the subacute inhalation observed adverse effect level (IOAEL). This subacute IOAEL represents a concentration at which similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential inter- and intra-species differences in sensitivity. The subacute IOAEL of 1,500 µg Mn/m^3 is provided for informational purposes only (TCEQ 2015).

The MOE between the subacute IOAEL and the 1-h acute ReV of 9.1 µg Mn/m^3 is a factor of 165, which would be a factor of 360 if a 6-h acute ReV had been developed instead (i.e., if a duration adjustment from 6 h to 1 h had not been conducted, providing a somewhat more appropriate MOE comparison). The MOE for the 24-h acute ReV of 5.0 µg Mn/m^3 is a factor of 300.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

When chronic toxicity factors are identified in the scientific literature or elsewhere (e.g., databases, ATSDR toxicological profiles), they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to develop chronic ReVs. If so, the TCEQ considers adoption of the published toxicity factor, with preference given to values that have undergone an external peer review and public involvement process. This process is the case for Mn, for which ATSDR derived a chronic inhalation MRL in 2012 (ATSDR 2012). A scientific literature search through October 2016 did not identify more appropriate key and supporting studies than those used by ATSDR to develop the chronic inhalation MRL. Additionally, ATSDR toxicological profiles and MRLs undergo internal agency review, a public comment period, and are externally reviewed by a peer review panel.

4.1.1 Key and Supporting Studies

4.1.1.1 Key Human Study - Roels et al. (1992)

Neurological effects from repeated inhalation exposure to Mn are well recognized as effects of high concern based on case reports and epidemiological studies of groups of occupationally exposed workers. A number of epidemiological studies have used batteries of neurobehavioral tests of neuromotor, cognition, and mood states to study the psychological or neurological effects of exposure to low levels of manganese in the workplace (ATSDR 2012). ATSDR utilized Roels et al. (1992) as the key study for derivation of the chronic inhalation MRL. The TCEQ will use the same key study and POD_{HEC} (benchmark dose or BMD) as ATSDR for derivation of the chronic ReV as an updated literature search did not identify a lower, reliable POD in humans (e.g., Zou et al. 2014 reported that occupational Mn exposure may be associated with cognitive impairment and decreased plasma brain-derived neurotrophic factor at ≥ 300 µg Mn/m^3 based on limited smelter area sampling; Kim et al. 2013 reported significantly increased locomotor activity in non-human primates exposed 2 h/day for 8 months to 1,950 µg Mn/m^3 as a constituent of welding fume, even after a 13-week recovery period; Hassani et al. 2012). Much of the text below was taken directly from ATSDR (2012).

Neurological effects of Mn exposure were evaluated in 92 male workers in a dry alkaline battery factory (Roels et al. 1992). The control group of 101 workers was age- and area-matched and not occupationally exposed to Mn but with similar work schedules and workloads. Total and respirable Mn dust concentrations were measured using personal air sampling in different occupational areas within the factory. Each worker's personal exposure was determined by the measured concentration characteristic for their particular job and the number of years employed. Workers were exposed for an average duration of 5.3 years (range 0.2-17.7 years) to average (geometric mean) concentrations of 0.215 and 0.948 mg Mn/m^3 in

respirable and total dust, respectively. The authors noted that the work processes had not changed significantly in the last 15 years, indicating that past exposures should be comparable to those measured in the study. Neurological function was measured using an audioverbal short-term memory test, a simple visual reaction time test using a chronoscope, and three manual tests of hand steadiness, coordination, and dexterity. This report provided good documentation of individual exposure data and characterization of the population studied.

Effects noted in study and corresponding doses: Mn-exposed workers performed significantly worse than the controls on the neurobehavioral tests, with particular differences in simple reaction time, eye-hand coordination, and hand steadiness. Dr. Harry Roels provided ATSDR with the data on the Mn-exposed group evaluated in this study. These data included individual exposure levels and whether the individual had an abnormal performance in the neurobehavioral tests (scores below the 5^{th} percentile score of the control group). Percent precision score in the eye-hand coordination test was the most sensitive endpoint among the endpoints showing statistically significantly elevated incidences of abnormal scores and was selected as the basis of the chronic MRL. Average exposure concentration for each worker was calculated by dividing the individual, lifetime-integrated respirable concentration (LIRD; calculated by Dr. Roels from occupational histories and measurements of workplace air Mn concentrations) by the individual's total number of years working in the factory. Individuals were grouped into six exposed groups and the control group, and the average of the range in each group was used in BMD modeling of the incidence data for number of workers with abnormal percent precision eye-hand coordination scores.

Available dichotomous models in the EPA BMD Software (version 1.1.1c) were fit to the incidence data for abnormal eye-hand coordination scores in workers exposed to respirable Mn. Based on the chi-square and Akaike's information criterion (AIC) measures of fit, all of the models provided adequate and comparable fits to the data. Estimates of the 95% lower confidence limit on the BMD ($BMDL_{10}$ values) from the different models showed an approximate 2-fold range for $BMDL_{10}$ values from 73 to 142 µg Mn/m^3 (BMD_{10} values ranged from approximately 110 to 189 µg Mn/m^3). The logistic model was the best fitting model (lowest AIC) and was used by ATSDR to provide the POD/$BMDL_{10}$ of 142 µg Mn/m^3 (associated BMD_{10} was 179 µg Mn/m^3) based on abnormal eye-hand coordination scores for derivation of the chronic MRL.

ATSDR used several BMD analyses of results from other epidemiological studies of neurobehavioral endpoints in Mn-exposed workers to support this POD (Clewell and Crump 1999, Clewell et al. 2003, Health Canada 2010). See Appendix A of ATSDR (2012) for more information. The TCEQ notes that this POD/$BMDL_{10}$ value (142 µg Mn/m^3) is very similar to the average $BMDL_{10}$ (190 µg Mn/m^3) across multiple neurological endpoints calculated by Clewell et al. (2003) for this same cohort (Roels et al. 1992, also that of Gibbs et al. 1999).

4.1.1.2 Consideration of Developmental/Reproductive Effects

The McGough and Jardine (2017) rat reproductive study is discussed in more detail above (Section 3.1.1.3). Briefly, the TCEQ cited various respiratory tract effects in rats due to chronic $MnCl_2$ exposure as well as:

- Statistically significant increases in lung weight following covariance analysis with body weight for *all* treated F0 females ($p<0.01$ at 6 mg/m^3, $p<0.001$ at 15 and 25 mg/m^3); and
- Statistically significant increases in kidney weight in F1 females at 10 and 17 mg/m^3 following covariance analysis with body weight ($p<0.05$ at 10 mg/m^3, $p<0.001$ at 17 mg/m^3).

Consideration of McGough and Jardine (2017) results suggests that a chronic LOAEL based on this study could be as low as 6 mg $MnCl_2$/m^3 (e.g., 2.6 mg Mn/m^3 based on lung weight and/or other respiratory tract effects) or 10 mg $MnCl_2$/m^3 (4.4 mg Mn/m^3 based on kidney weight). However, these *potential* animal PODs:

- Are approximately 18-31 times higher than that based on the preferred human data ($BMDL_{10}$ of 0.142 mg Mn/m^3);
- Would result in a higher POD_{HEC} associated with greater uncertainty compared to the human-based/duration-adjusted POD_{HEC} of 0.0507 mg Mn/m^3, which is approximately 5-9 times lower (e.g., 2.6-4.4 mg Mn/m^3 $\times$ 6 h per day/24 h per day $\times$ 7 days per week/7 days per week = 0.65-1.1 mg Mn/m^3 $\times$ RDDR $\approx$ 4 = duration-adjusted POD_{HEC} of $\approx$ 2.6-4.4 mg Mn/m^3 / maximum UF_L of 10 = 0.26-0.44 mg Mn/m^3); and
- Do not identify the critical effects (neurological in this case) based on the existing subchronic/chronic database.

Lastly, the TCEQ prefers use of human data in deriving toxicity factors, and the key study (Roels et al. 1992) used for the chronic ReV is a human study.

Developmental studies on the potential effects of the inhalation or ingestion of Mn compounds are very limited, particularly in humans, although the limited oral human studies available support the hypothesis that Mn exposure may be detrimental to childhood neurodevelopment (ATSDR 2012). See the discussion of the Hamai et al. (2006) rat study (acute/subacute exposure) in Section 3.1.1.2.3 and Lown et al. (1984) in Section 3.1.1.3. Briefly, Lown et al. (1984) found that pups raised by foster mothers that had been exposed to 61 mg Mn/m^3 pre-conception and filtered air post-conception had reduced weights compared to pups raised by foster mothers exposed only to filtered air. This LOAEL (61 mg Mn/m^3) for reduced pup body weight, after application of a maximum UF_L of 10, is 43-fold higher than the human subchronic POD ($BMDL_{10}$ of 0.142 mg Mn/m^3) used by the TCEQ for derivation of the chronic ReV and would result in a much higher POD_{HEC}. Oral developmental rat studies involving gestational and postnatal exposure combined (to some extent) provide neurological LOAELs as low as 4.4-8 mg/kg-day (e.g., significant ($p<0.05$), dose-related gliosis in the brains of rat pups in Lazrishvili

et al. 2009; hematological changes indicative of iron deficiency in dams and pups and increased levels of the inhibitory neurotransmitter GABA in pup brains in Garcia et al. 2006). As a simple example assuming similar absorption across routes, the air concentration corresponding to a rat oral dose of 4.4 mg Mn/kg-day would be 5 mg Mn/m^3 (i.e., 4.4 mg Mn/kg-day $\times$ 0.25 kg = 1.1 mg Mn/day / 0.22 m^3/day = 5 mg Mn/m^3), which after application of a maximum UF_L of 10 is 0.5 mg Mn/m^3, approximately 3.5-fold higher than the human subchronic POD ($BMDL_{10}$ of 0.142 mg Mn/m^3) used for derivation of the chronic ReV. Moreover, the fact that non-human primates are very sensitive to the neurological effects of Mn is critically important, especially considering that rodent models do not exhibit the same neurological symptoms as humans and monkeys despite high doses through inhalation, oral, and intravenous routes (ATSDR 2012). *Thus, due to this apparent difference in susceptibility in humans/non-human primates versus rodents, these rodent results do not necessarily assuage potential developmental neurological concerns for humans.* Study evaluations of appropriate and sensitive developmental neurological endpoints (in rodent assays or humans) by both the inhalation and oral routes are needed as Mn-induced neurological effects are a primary concern based on the existing database.

4.1.2 Adjustments to the POD

4.1.2.1 Dosimetry

4.1.2.1.1 Duration Adjustments

The duration-adjusted POD was calculated as follows, consistent with TCEQ (2015):

$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)
VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)
$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)
$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

POD_{HEC} = 142 µg Mn/m^3 × 10 m^3/20 m^3 × 5 days/7 days = 50.7 µg Mn/m^3

4.1.2.2 UFs

The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive ReVs (i.e., assume a threshold MOA; TCEQ 2015). A total UF of 60 was applied to the POD_{HEC} of 50.7 µg Mn/m^3 to derive the chronic ReV: a UF_H of 10 as well as a UF_D of 6. The following is more specific concerning the rationales for the applicable UFs, which are generally consistent with ATSDR (2012):

- A full UF_H of 10 was used to account for potential intrahuman variability (e.g., possibly enhanced susceptibility of the young with increased permeability of neuronal barriers, children with portosystemic shunt, the elderly, individuals with chronic liver disease such as cirrhosis of the liver or parenteral nutrition, individuals with pre-existing neurological disease, women and others with iron deficiency and higher blood Mn; O'Neal and Zheng 2015);
- A UF_{Sub} value > 1 is not necessary to extrapolate from subchronic exposure (mean of 5.3 years, with exposure durations of up to 17.7 years) to chronic exposure in this case (e.g., Clewell et al. 2003 indicate that duration of exposure in the key study was not significantly correlated with any measure of psychomotor response and BMDL values from the chronic Gibbs et al. 1999 worker study were similar, the UF_{Sub} is also interrelated with the UF_D for which a conservative value of 6 was used), so a value of 1 was used (consistent with ATSDR 2012 not using a UF_{Sub}); and
- A UF_D of 6 was used for limitations and uncertainties in the database including the lack of epidemiological data for humans chronically exposed to soluble forms of Mn and the concern that the general population may be exposed to more soluble forms of Mn than most of the Mn-exposed workers in the key and supporting studies. Several rat studies indicate that inhalation of more soluble forms of Mn (e.g., manganese sulfate, manganese chloride) results in higher Mn brain concentrations than inhalation of less soluble forms (e.g., manganese phosphate, manganese dioxide) (Dorman et al. 2001, 2004 and Roels et al. 1997 as cited by ATSDR 2012). Additionally, although the neurological system is the most sensitive target organ identified by the existing database for effects from subchronic- to chronic-duration inhalation exposure to Mn, data are lacking to fully characterize the potential risk for all organ systems from chronic inhalation exposure (ATSDR 2012). Database limitations in regard to more soluble forms of Mn, combined with the lack of a robust developmental database (e.g., limited developmental study information, especially by inhalation for longer durations) and the consideration that rodents may be a less-than-desirable model for neurological effects (i.e., rodent models do not appear to be as susceptible to Mn-induced neurotoxicity as humans and monkeys, somewhat diminishing the relevance of chronic Mn inhalation exposure rodent neurological results in regard to their ability to help identify the most sensitive Mn effects that may occur in humans), results in a medium confidence in the database overall (TCEQ 2015).

Table 7. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Summary
Key Study	Roels et al. (1992)
Study Population	Humans
Study Quality Confidence Level	Medium
Exposure	Occupational
Critical Effect	Abnormal eye-hand coordination scores
Exposure Duration	Mean of 5.3 years (with exposure durations of up to 17.7 years)
POD	142 µg Mn/m^3 ($BMDL_{10}$)
POD_{HEC} (continuous)	50.7 µg Mn/m^3 (POD adjusted for duration)
Total uncertainty factors (UFs)	60
Intraspecies UF	10
Subchronic UF	1
Database UF *Database Quality*	6 Medium
chronic ReV (HQ = 1)	**0.84 µg Mn/m^3**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.25 µg Mn/m^3**

ATSDR (2012) did not have the benefit of the McGough and Jardine (2017) reproductive study, and used a UF_D of 10. Consequently, the chronic ReV is higher than the chronic inhalation MRL. However, the $^{chronic}ESL_{threshold(nc)}$, rounded up to one significant figure, is identical to the chronic inhalation MRL (ATSDR 2012).

4.1.3 Implications of Recent PBPK Modeling Studies

Experimental animal studies and occupational human studies strongly suggest a link between increased Mn concentrations in brain (specifically in the globus pallidus) and reported subclinical or clinical neurological outcomes in exposed subjects (Ramoju et al. 2017). Thus, Mn concentration in the globus pallidus has been utilized as the target tissue dose by several PBPK studies for tissue dose-based assessments. More specifically, there have been several PBPK studies published relatively recently with implications for using standard default methods to derive chronic toxicity factors, including the chronic ReV (e.g., Ramoju et al. 2017, Gentry et al. 2017, Taylor et al. 2012). Example implications include (but are not limited to):

- A UF_H of 10 not being necessary for Mn-induced neurological effects since no life-stage (i.e., fetal, neonate, pregnant or non-pregnant female) achieved a higher globus pallidus AUC than adult males and a toxicokinetic chemical-specific adjustment factor (CSAF) of ≈ 1.25 may suffice for sensitive subgroups such as those with hepatobiliary dysfunction (e.g., $UF_{H\text{-}TD}$ of 3.16 × CSAF of 1.25 = 4) (Taylor et al. 2012);
- Brain concentration (i.e., globus pallidus as the most sensitive region for Mn accumulation) is predicted not to be entirely linearly-related to ambient air concentration, particularly at lower air concentrations, and conventional conversion of occupational-to-equivalent continuous environmental concentrations is not reported to be appropriate for Mn-induced neurological effects (e.g., see Figure 8 of Gentry et al. 2017);
- ATSDR's occupational POD/$BMDL_{10}$ of 142 µg Mn/m^3 corresponds to a predicted globus pallidus concentration of just over 0.6 µg Mn/g tissue, which is at the very upper end of the range of reportedly "healthy" individual background concentrations (based on data from general post-mortem studies) (Ramoju et al. 2017), consistent with a UF_L not being necessary when a $BMDL_{10}$ is utilized as the POD (TCEQ 2015);
- Background brain (i.e., globus pallidus) concentrations begin an upward inflection at continuous exposure concentrations between 1 and 10 µg Mn/m^3, with the slope increasing more rapidly from 10 µg Mn/m^3 through about 100 µg Mn/m^3 or so, suggesting a lower end threshold for brain Mn accumulation of approximately 1 µg Mn/m^3 (see Figure 7 of Taylor et al. 2012); and
- Health effects would not be expected at ambient air concentrations that PBPK modeling indicates do not result in an increase in brain concentrations (Gentry et al. 2017).

However, individual findings should not be blindly utilized in this case to refine specific aspects of a standard assessment (e.g., UF_H) while ignoring the bottom-line risk assessment results available from the PBPK studies themselves, which can be used to evaluate the reasonableness of the chronic ReV derived above through standard methodology not utilizing PBPK modeling.

The TCEQ agrees that Mn-induced neurobehavioral effects would not be expected at long-term ambient air concentrations that do not result in an increase in brain concentrations. Results from the Gentry et al. (2017) PBPK study suggest that at environmental air concentrations of respirable Mn similar to the chronic ReV and ESL (i.e., < 1 µg Mn/m^3), Mn concentrations in the brain (i.e., globus pallidus) would be similar to background (see Figure 8 and Tables 3 and 4 of the study). Likewise, the chronic ReV and ESL (0.84 and 0.25 µg Mn/m^3) are below continuous air concentrations predicted to increase brain concentrations in human fetuses (10 µg Mn/m^3) and nursing infants (1 µg Mn/m^3) (Yoon et al. 2011 as cited by ATSDR 2012). *Thus, as 1 µg Mn/m^3 is the estimated lower end, continuous daily exposure threshold for brain Mn accumulation and this value is very similar to the chronic ReV of 0.84 µg Mn/m^3, recent PBPK studies support the chronic ReV as health protective without being unduly conservative, regardless of the particular POD and procedures employed in its derivation.*

4.2 Carcinogenic Potential

No human or laboratory animal inhalation carcinogenicity studies were identified for Mn or inorganic Mn compounds in the scientific peer-reviewed literature. As such, *data are inadequate for an assessment of human carcinogenic potential*, and no further evaluation of carcinogenic potential (e.g., weight of evidence, dose-response assessment) is possible and/or necessary (TCEQ 2015).

4.3 Welfare-Based Chronic ESL

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne Mn.

4.4 Chronic Values for Air Permitting and Air Monitoring Evaluations

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

- chronic ReV = 0.84 µg Mn/m^3
- $^{chronic}ESL_{threshold(nc)}$ = 0.25 µg Mn/m^3

The chronic ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 0.25 µg Mn/m^3 (Table 2). The chronic ReV of 0.84 µg Mn/m^3 will be used for evaluation of long-term ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) value is not used to evaluate ambient air monitoring data.

4.5 Chronic Noncarcinogenic IOAEL

Neurological effects are sensitive endpoints of long-term Mn exposure in occupationally exposed workers. An approximate environmental air concentration of 17 µg Mn/m^3 corresponds to a 10% extra risk concentration (ERC_{10} of 0.55 µg Mn/g tissue) for any adverse neurological response based on categorical regression modeling between human globus pallidus Mn concentration and severity-scored neurological outcomes from eight epidemiological studies (Ramoju et al. 2017) based on the PBPK modeling results of Gentry et al. (2017) (i.e., 17 µg Mn/m^3 was interpolated based on tissue concentration results for 10 and 20 µg Mn/m^3 in Table 3 of Gentry et al. 2017). Thus, the chronic environmental air concentration of 17 µg Mn/m^3 predicted to result in the ERC_{10} can be considered a chronic IOAEL (like a BMD_{10}) under TCEQ guidelines (TCEQ 2015). This value represents a concentration at which similar effects could occur in some individuals exposed chronically to this level (or greater). Importantly, adverse effects are not a certainty due to potential intraspecies differences in sensitivity. The MOE is a factor of 20 between the chronic IOAEL and the chronic ReV.

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