Oregon Department of Environmental Quality

Framing Document for DEQ's Air Toxics Science Advisory Committee

Petition for Changes to DEQ's Manganese Toxicity Reference Value for Acute Exposure

Overview

The Oregon Department of Environmental Quality (DEQ) and Oregon Health Authority (OHA) are currently reviewing the inhalation toxicity reference values (TRVs) used in DEQ's air quality programs. Existing TRVs are in Oregon Administrate Rule (OAR, 340-247-8010 Table 2). As part of the TRV review process, DEQ OARs give an option for members of the public to submit petitions to suggest TRV updates. DEQ welcomed petitions for consideration during the current TRV update process. Petitions were due in late 2022.

DEQ received one petition to change DEQ's TRV for acute exposure (24-hour) to manganese (Bridgewater Group, 2022). Hereafter, this TRV is referred to as the "**acute TRV**". This petition was prepared by Bridgewater Group, a consulting firm that works extensively with sources in Oregon on air quality permitting actions, including Cleaner Air Oregon Risk Assessments. The toxicological information and analysis for the petition was provided by ToxStrategies, a scientific consulting firm that provides information to address regulatory issues. The petition proposes to increase the DEQ acute manganese TRV from 0.3 µg/m^3 to 5 µg/m^3, which is consistent with the 24-hour ambient monitoring comparison value developed by the Texas Commission of Environmental Quality (TCEQ, 2017). While the TRV proposed in the petition is equivalent to the TCEQ TRV, the petition proposes a slightly different set of uncertainty factors (UFs) than the ones used by TCEQ, which are discussed in detail further in this document.

Staff at ToxStrategies also published a peer-reviewed manuscript titled "Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese" in *Regulatory Toxicology and Pharmacology* (Perry et al., 2023); hereafter, referred to as "**Perry et al.**". This manuscript states that the work was supported by Gunderson, LLC, of Portland, OR and Cascade Steel Rolling Mills, Inc, of McMinnville, OR. The manganese acute TRV proposed in Perry et al. is also equivalent to the TCEQ TRV and petition TRV; however, Perry et al. proposes yet another slightly different set of uncertainty factors than the ones used by TCEQ and the petition, which are discussed in detail further in this document.

DEQ is seeking feedback from ATSAC on this petition. DEQ does not have a final proposal yet for changes to DEQ's acute manganese TRV. ATSAC member feedback will inform DEQ's proposal. This framing document provides summary information for ATSAC members to prepare for a discussion and includes key questions that DEQ will ask ATSAC members at the next ATSAC meeting.

DEQ's Request for ATSAC Members

1) Read the petition DEQ received for the acute manganese TRV (link).
2) Read Perry et al. 2023 "Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese" (link).
3) Read this framing document for DEQ's initial thoughts on and questions about the petition. This framing document is meant to be supplemental to the petition, so it does not summarize all the background information that the petition includes.
4) Prepare answers to the questions at the end of this framing document, which we will discuss at our next ATSAC meeting. Kearns & West will reach out soon to schedule a meeting.

Here are supplemental documents that may help you prepare for the discussion. Please note that the petition includes its own supplemental information as appendices (*e.g.*, Dorman et al. 2005).

- TCEQ Guidelines to Develop Toxicity Factors (TCEQ, 2015)
- TCEQ Developmental Support Document on Manganese and Inorganic Manganese Compounds (TCEQ, 2017)
- California's Office of Environmental Health Hazard Assessment (OEHHA) Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries: Manganese and Compounds Reference Exposure Levels, starts on page 434 (OEHHA, 2008b)

If you have additional information that you would like other ATSAC members to consider, please submit it to DEQ well in advance of the ATSAC meeting so that others have sufficient time to review.

TRV Background

As a reminder, DEQ uses the term TRV when referring to similarly derived health-based toxicity values developed by other agencies. Additional background information on TRVs and the TRV update process can be found in these fact sheets: Proposed TRV Update and Selection Process for ATSAC Review and Updates after the ATSAC Meeting. Oregon Administrative Rules (OARs), adopted by the Oregon Environmental Quality Commission (EQC), specify sources of toxicity information considered to be authoritative in terms of their scientific rigor and comprehensive methods for producing toxicity information (OAR 340-247-0030). Authoritative sources for acute exposure (24-hour) TRVs include the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) and California Environmental Protection Agency (CalEPA). DEQ in consultation with ATSAC can also propose an acute exposure TRV for the EQC to consider, which gives DEQ flexibility in choosing and setting acute TRVs that best match our 24-hour exposure duration definition.

Changing DEQ's Prior Acute Value for Manganese

DEQ's existing manganese acute TRV is based on a chronic exposure TRV from CalEPA's Office of Environmental Health and Hazard Assessment (OEHHA). The critical study reported neurotoxicity in workers exposed to manganese for an average of 5.3 years and up to 17 years (Roels et al., 1992). In agreement with the petition, DEQ acknowledges that deriving acute TRVs from chronic TRVs is not ideal and, where appropriate and possible, DEQ would prefer to derive an acute TRV from a study with an acute exposure duration. DEQ states in the TRV update fact sheet that DEQ and OHA would prioritize finding alternative TRVs that are based on studies with short-term/acute exposure periods during its review of acute TRVs. The petition goes into detail on the lack of manganese acute TRVs available from DEQ's authoritative sources.

DEQ agrees that TCEQ's manganese acute TRV is a good resource because (1) TCEQ's acute TRVs match DEQ's acute exposure time (24 hours), (2) TCEQ's manganese acute TRV is based on short-term toxicity study data, and (3) TCEQ provides comprehensive developmental support documentation. The following pages of this framing document outline and compare the toxicity information used in TCEQ's developmental support document, the petition, and Perry et al. (2023).

As shown in Table 1, both TCEQ and the petition use the same critical study (Dorman et al., 2005). Perry et al. (2023) uses two critical studies (Dorman et al., 2005; Erikson et al., 2008). Perry et al. states "reversible bronchiolitis (Dorman et al., 2005) and biochemical markers of oxidative stress in the brain (decreased GSH and reversible increased GS protein with decreased gene expression) (Erikson et al., 2008) in monkeys, following 90 h of exposure, is considered the most relevant POD" (2023).

TCEQ, the petition, and Perry et al. all use the same point of departure (POD) value (Table 1).

Table 1. Information on the critical studies used in the TRVs for acute exposure to manganese.

	Critical Study Author and Year	Critical Study Species	Critical Effect Target Organ	Description of TRV Critical Effect	Duration of Exposure in Critical Study	Point of Departure (POD) Method	POD Value (mg/m^3)
Used in TCEQ, Petition, and Perry et al., 2023	**Dorman et al. 2005**	Male Rhesus Monkeys (20-24 months)	Respiratory System	Inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation)	6 hrs/day, 5 days/week, 15 exposure days*	Lowest observed adverse effects level (LOAEL)◊	1.5
Used in Perry et al., 2023	**Erikson et al. 2008** in addition to Dorman et al. 2005	Male Rhesus Monkeys (20-24 months)	Nervous System	Biochemical markers of oxidative stress in the brain (decreased glutathione levels and reversible increased glutamine synthetase protein with decreased gene expression)	6 hrs/day, 5 days/week, 15 exposure days†	LOAEL	1.5

*In Dorman et al., young male rhesus monkeys were exposed to $MnSO_4$ through inhalation exposure for 6 hrs/day for 5 days/week. One cohort of monkeys (*n*=4-6 animals per exposure concentration) was exposed to $MnSO_4$ in air at 0.06, 0.3, or 1.5 mg Mn/m^3 for 65 exposure days (2005). Another eight monkeys were exposed to $MnSO_4$ at 1.5 mg Mn/m^3 for 65 days and held for 45 or 90 days before evaluation. A second cohort (*n*=4 monkeys per time point) was exposed to $MnSO_4$ at 1.5 mg Mn/m3 and evaluated after 15 or 33 exposure days. Evaluations included measurement of lung manganese concentrations and evaluation of respiratory histologic changes (Dorman et al., 2005).

◊Effects were subclinical. Changes were only apparent on post-mortem histopathological exam.

†In Erikson et al., young male rhesus monkeys in the control group (n=6) were exposed to filtered air for 65 exposure days (*n*=6) (2008). The exposure group monkeys in Erikson et al. were exposed to $MnSO_4$ through inhalation exposure at 1.5 mg Mn/m^3 for 15 (*n*=4) or 33 (*n*=4) exposure days; or to 1.5 mg Mn/m^3 for 65 exposure days and held for either 45 days (*n*=4) or 90 days (*n*=4) before evaluation (recovery groups). The authors assessed biochemical endpoints indicative of oxidative stress and excitotoxicity in the cerebellum, frontal cortex, caudate, globus pallidus, olfactory cortex, and putamen. Glutamine synthetase (GS), glutamate transporters (GLT-1 and GLAST) and tyrosine hydroxylase (TH) protein levels, metallothionein (MT), GLT-1, GLAST, TH and GS mRNA levels, and total glutathione (GSH) levels were determined for all brain regions (Erikson et al., 2008).

While TCEQ, the petition, and Perry et al. all use the same POD, the TRVs from TCEQ, petition, and Perry et al. use different uncertainty factors to calculate a 24-hour acute manganese TRV (Table 2). Quotes from TCEQ on their UF selections are displayed in Table 3.

Table 2. Information on the uncertainty factors (UFs) and other adjustments used in TCEQ's, the petitioner's, and Perry et al.'s TRV for acute exposure to manganese.

TRV Source	TRV ug/m^3	Uncertainty Factor (UF) Information						Human Equivalent Concentration in TRV?	Time Adjustment in TRV?
		UF_A Inter-species	UF_H Intraspecies	UF_L LOAEL	UF_S Sub-chronic	UF_D Database	Total UF		
TCEQ, 2017	5.0	3	10	2	NA	6	300*	No	No◊
Petition	5.0	10†	10	3	NA	--	300	No	No
Perry et al., 2023	5.0	3‡	10	10‡	NA	--	300	No	No

*While the total UF is equivalent 360, TCEQ used a total UF of 300 when calculating the TRV. TCEQ has a policy that 300 is the maximum total UF allowed for acute TRVs.

◊TCEQ stated "For the 24-h ReV, the LOAEL/POD of 1.5 mg Mn/m^3 was used as the 24-h PODADJ 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 PODADJ for derivation of the 24-h ReV is 1.5 mg Mn/m^3" (2017).

†The petition states "a lower 3-fold interspecies uncertainty factor could also be supported because a dosimetric adjustment between moneys and humans is not required as discussed in Dorman et al. (2005). Using a 10-fold factor, the proposed TRV is conservative" (Bridgewater Group, 2022).

‡Perry et al. states that they applied a 3-fold factor for UF_A, which includes 3-fold for differences in toxicodynamics and a factor of 1 for toxicokinetic differences (2023). The authors also state that the 10-fold UF_L accounts for both LOAEL-to-NOAEL extrapolation and the lack of data for a continuous 24-h exposure period (Perry et al., 2023).

Table 3. TCEQ's statements on the uncertainty factors (UFs) for manganese.

UFs	Page Number of the TCEQ Manganese Document	Direct Quote from TCEQ (2017)
UF_A Interspecies	21	"A UF_A of **3** was used to account for potential toxicodynamic differences between rhesus monkeys and humans."
UF_H Intraspecies	21	"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)."
UF_L LOAEL	8	"…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/m3) 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)."
	21	"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"
UF_S Subchronic		NA
UF_D Database	21-22	"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)."

Proposal for New Acute Manganese TRV

DEQ does not have a final proposal for acute exposure TRV. To aid ATSAC discussion, Table 4 outlines a range of potential proposals for DEQ's acute manganese TRV. Not all potential options are in this table. **DEQ wants to hear from ATSAC members on the benefits and drawbacks of the proposals in Table 4.** DEQ also wants to know if ATSAC members think a better proposal option is available other than those listed in Table 4. ATSAC member feedback will inform DEQ's final proposal.

Table 4. Potential options for DEQ's acute manganese TRV for ATSAC to discuss.

TRV Proposal Name	TRV (ug/m^3)	Uncertainty Factor (UF) Information						Human Equivalent Concentration in TRV?	Time Adjustment in TRV?	Notes
		UF_A Inter-species	UF_H Intra-species	UF_L LOAEL	UF_S Sub-chronic	UF_D Database	Total UF*			
Option 1 TCEQ	5.0	3	10	2	NA	6	300	No	No	No changes to TCEQ's 2017 final acute Mn TRV. This includes TCEQ's policy that 300 is the maximum total UF allowed for acute TRVs.
Option 2 TCEQ with no total UF maximum	4.2	3	10	2	NA	6	360	No	No	Removes TCEQ's policy of capping the total UFs to 300 for acute TRVs.
Option 3 Petition	5.0	$10^{\lozenge}$	10	3	NA	--	300	No	No	The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.
Option 4 Petition with UF_D	0.8	10	10	3	NA	6	1800	No	No	Compared to the petition, includes an additional UF_D, which matches the TCEQ UF_D.
Option 5 Petition with UF_D and lower UF_A	2.8	3	10	3	NA	6	540	No	No	Compared to petition, includes the additional database UF_D, but a lower UF_A.
Option 6 Perry et al. 2023	5.0	3	10	10	NA	--	300	No	No	The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.
Other Suggestions from ATSAC members										**Please let DEQ know if you think there is another good option that is not already on this table.**

*Additional options include rounding the total UF to one significant digit (*e.g.*, the total UF for Option 2 would be 400 instead of 360). DEQ has observed that this is regularly done by U.S. EPA and ATSDR.

Agency Policy on UFs

Different agencies have different UF recommendations. The TCEQ Guidelines Document includes a table that lists the default UFs recommended by different agencies including the U.S. EPA and ATSDR (TCEQ, 2015). A copy of this table is in Appendix A.

Policies on Maximum Total UFs

TCEQ has a policy that 300 is the maximum total UF allowed for acute TRVs if three UFs are used and the cumulative UF exceeds 300 (TCEQ, 2015). DEQ is not aware of other authoritative source agencies having a policy like this to cap total UFs for acute TRVs at 300. One TRV option for the manganese acute exposure TRV (option 2 in Table 2) is to remove TCEQ's policy cap of 300 and apply a total UF of 360 instead.

LOAEL Uncertainty Factor (UF_L) Considerations

As seen in the Appendix A, UF_L is an example of how different agencies have different UF approaches. TCEQ uses a UF_L of 2 to 3 for the LOAEL when the health outcome is mild (TCEQ, 2015); in the case of manganese, TCEQ selected a UF_L of 2 (Table 3). The CalEPA states that a UF_L of 6 can be used when mild effects are used to derive an acute Reference Exposure Level (OEHHA, 2008a). The ATSDR uses a UF_L of 3 when there is a "minimal LOAEL," which is described as minimal effects that represent an early indication of toxicity (Chou et al., 1998).

Database Uncertainty Factor (UF_D) Considerations

One key difference between the petition and TCEQ is the absence of a UF_D database uncertainty factor in the petition. Perry et al. also does not include a UF_D. Table 3 includes TCEQ's reasoning for including a UF_D of 6, including the need for additional studies to investigate the potential for developmental neurological effects. TCEQ states "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)" (TCEQ, 2017).

DEQ thinks there are several unknowns related to manganese-related neurodevelopmental toxicity that a UF_D may help protect against. While OEHHA did not develop an acute exposure TRV for manganese due to lack of studies, OEHHA does provide information on why the potential for developmental neurological issues from manganese is a concern (OEHHA, 2008b). OEHHA states that several epidemiology studies have reported correlations between early life exposure to excessive manganese and symptoms of impaired neurodevelopment as revealed on neurobehavioral tests and in poorer academic performance [pg. 451-452; (OEHHA, 2008b)]. For example, in a prospective study of the neurobehavioral effects of *in utero* exposure to manganese, Takser et al. reported an inverse correlation between cord blood manganese at birth and three subscales of psychomotor development (McCarthy scales of children's abilities) measured at three years of age (n= 126): attention (partial $r = -0.33$, $p < 0.01$), nonverbal memory (partial $r = -0.28$, $p < 0.01$), and hand skills [partial $r = -0.22$, $p < 0.05$; (OEHHA, 2008b; Takser et al., 2003)].

OEHHA also highlights eight reasons why children may be more susceptible to manganese toxicity than adults [pg. 461; (OEHHA, 2008b)]. Here are three examples:

- "The newborn's brain is still developing, myelination is incomplete, and the blood-brain barrier is not fully formed (Chan et al., 1992). These conditions facilitate manganese uptake into the central nervous system and increase the risk of attaining toxic levels."
- "The liver of newborns has not yet developed the ability to maintain safe levels of manganese in the bloodstream and brain tissues by excreting excess manganese in the bile, i.e., homeostasis of manganese has not yet developed (Miller et al., 1975)."

- "Manganese exposures in childhood are associated with impaired neurodevelopment including decrements in intellectual function. Thus, a major toxicodynamic factor that differs between adults and children, namely development of the central nervous system, presents hypersensitive targets for toxicity in the developing infant and child."

The petitioners state that their proposed TRV (option 3 in Table 4) is protective of respiratory toxicity and that additional uncertainty factors for reproductive and developmental toxicity are unnecessary because of:

1. **Reproductive and Developmental Rat Study:** "The reproductive and developmental toxicity study by McGough and Jardine (2017) involving subchronic exposures in rats at levels much higher than the proposed TRV (up to 8.1 mg/m^3 for up to 714 hours) did not result in reproductive or developmental toxicity, which reduces uncertainty associated with potential reproductive or developmental effects" (Bridgewater Group, 2022).
2. **Neurotoxicity Primate Study:** "Additionally, Dorman et al. (2006b) reported no observable symptoms of neurotoxicity associated with exposures in the 2005 study" (Bridgewater Group, 2022).
3. **PBPK Modeling:** "To further address any uncertainty as to whether neurotoxicity could pose a hazard to humans at the proposed TRV, we used the current human PBPK model to evaluate two exposure scenarios: reoccurring exposures for monthly 24-hour exposures (monthly scenario), and continuous exposure for 3 weeks at the age when manganese levels in brain are predicted to be highest (three week scenario). For both scenarios, the current human PBPK model was used to predict concentrations of manganese in blood, liver, and globus pallidus in males and females. The model predictions indicate that, at all life stages, the levels of manganese in the target tissue of the globus pallidus do not increase significantly over background levels and are lower than tissue NOAELs in the globus pallidus" (Bridgewater Group, 2022).

1. Reproductive and Developmental Rat Study

However, McGough and Jardine do not evaluate neurodevelopmental endpoints (2017), the developmental endpoint of concern highlighted by epidemiology studies and OEHHA's assessment. McGough and Jardine looked for $MnCl_2$ effects on rat body weight, food consumption, and effects on the entire reproductive system including maternal care. The authors also monitored the survival and growth of the rat's offspring up to weaning. The authors do measure brain weight, which they conclude "brain weight did not achieve significance and therefore was not positively attributed to treatment" (McGough and Jardine, 2017), but they do not evaluate neurodevelopmental endpoints.

2. Neurotoxicity Primate Study

Dorman et al. (2006b) was similar to Dorman et al. (2005) where young male rhesus monkeys were exposed to $MnSO_4$ through inhalation exposure. Dorman et al. (2006b) reported an association between magnetic resonance imagining (MRI) changes and pallidal manganese concentration in rhesus monkeys following subchronic $MnSO_4$ inhalation exposure. However, Dorman et al. (2006b) did not evaluate the neonatal human exposure period of greatest concern, and the study was not designed to evaluate neurodevelopmental outcomes, such as very early life exposures leading to persistent cognitive deficits.

3. PBPK Modeling

It is DEQ's understanding that the PBPK model was developed based on the assumption that the globus pallidus is the target tissue for all relevant manganese toxicity in the brain. The petition and Perry et al. state that the globus pallidus is the area of the brain with the highest levels of manganese accumulation following exposure, which is demonstrated in a couple of studies (see Table 6.3.1 in OEHHA, 2008b). However, studies also show that there are other areas of the brain that also accumulate manganese after exposure, though it is at lower levels than the globus pallidus. For example, in Dorman et al. (2006a), even at the lowest dose (60 µg/m^3) in rhesus monkeys, manganese levels were significantly elevated in four of the eight brain regions examined, globus pallidus, putamen, white matter and cerebellum (OEHHA, 2008b).

Dose response data from studies that petitioners cite correlate globus pallidus manganese concentrations with effects such as hand-eye coordination issues and structural changes to the globus pallidus. DEQ was not able

to find studies that showed correlations between globus pallidus manganese concentrations and the cognitive deficits observed in children that were exposed during the neonatal period. Therefore, while the globus pallidus has been shown to have the highest amount of manganese in the brain following manganese exposure, DEQ does not think there are enough studies currently to know for sure:

- Whether the globus pallidus is the relevant target tissue for neurodevelopmental effects such as impaired cognition following early life exposure
- How much manganese is needed in each brain region to cause neurodevelopmental effects
- What developmental stages are most susceptible to Mn insult
- How long early life exposures need to be to cause neurodevelopmental effects

These are the types of unknowns that a UF_D protects against. For example, is it possible for manganese inhalation exposure to lead to neurodevelopmental effects from a 24-hour exposure to an area of the brain that is not the globus pallidus at a lower dose than what causes other types of health effects? Is it possible for the mechanism by which manganese may cause developmental neurotoxicity in children is different from the mechanism by which manganese causes the hand-eye coordination and other subtle/transient neurotoxicity in adult workers (as observed in the Roels et al. 1992 study that underlies the chronic noncancer TRV)? DEQ still has these questions.

DEQ's priority is to make sure that the manganese acute TRV is health protective, especially for vulnerable populations such as children during critical developmental windows. DEQ wants to hear from ATSAC members if petitioners provide enough information to ensure that a reduced or absent database uncertainty factor remains health protective for developing children.

Key Questions for ATSAC

1) UF_A: Do you think the UF_A should be 3 or 10 or something else? Why?
2) UF_H: Do you think the UF_H should be 10 or something else? All proposals in Table 4 have a UFH of 10.
3) UF_L: Do you think the UF_L should be 2, 3, 10, or something else? Why?
4) UF_D: Do you agree with the petitioners that there is enough evidence to <u>not</u> have a database uncertainty factor? Why or why not?
    - Do you agree with the TCEQ database UF of 6? Why or why not?
5) Total UF: Do you think we should put a cap on the maximum total UF like TCEQ does?
6) What proposal option in Table 4 do you like the best and why? If you do not like any of the options listed in this document, why? Would you propose another option for DEQ to consider? Is there other information that DEQ needs to consider in order to choose a proposal option?

Next Steps

ATSAC member feedback will inform DEQ's proposal for the acute manganese TRV. Kearns & West staff will be in contact soon to set up an ATSAC meeting to listen to ATSAC member's thoughts on the petition and the discussion questions in this framing document. The petitioners will also be invited to attend this ATSAC meeting to give a short overview presentation of the petition. If you have questions or initial feedback, please email Apollonia Goeckner, apollonia.goeckner@deq.oregon.gov.

References

ATSDR, 2012. Toxicological Profile for Manganese.

Bridgewater Group, 2022. Supporting Evidence for Petition for Oregon Department of Environmental Quality (ODEQ) Air Toxics Review to Revise the Acute Toxicity Reference Value (TRV) for Acute Manganese Exposure.

Chan, A.W., Minski, M.J., Lim, L., Lai, J.C., 1992. Changes in brain regional manganese and magnesium levels during postnatal development: modulations by chronic manganese administration. Metab. Brain Dis. 7, 21–33.

Chou, C.-H.S.J., Holler, J., De Rosa, C.T., 1998. Minimal risk levels (MRLs) for hazardous substances. J Clean Technol Env. Toxicol Occup Med 7, 1–24.

Dorman, D.C., Struve, M.F., Gross, E.A., Wong, B.A., Howroyd, P.C., 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. Respir. Res. 6, 1–10.

Dorman, D.C., Struve, M.F., Marshall, M.W., Parkinson, C.U., James, R.A., Wong, B.A., 2006a. Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. Toxicol. Sci. 92, 201–210.

Dorman, D.C., Struve, M.F., Wong, B.A., Dye, J.A., Robertson, I.D., 2006b. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. Toxicol. Sci. 92, 219–227.

Erikson, K.M., Dorman, D.C., Lash, L.H., Aschner, M., 2008. Duration of airborne-manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. Neurotoxicology 29, 377–385.

McGough, D., Jardine, L., 2017. A two-generation inhalation reproductive toxicity study upon the exposure to manganese chloride. Neurotoxicology 58, 194–202.

Miller, S.T., Cotzias, G.C., Evert, H.A., 1975. Control of tissue manganese: initial absence and sudden emergence of excretion in the neonatal mouse. Am. J. Physiol.-Leg. Content 229, 1080–1084.

OEHHA, 2008a. Air Toxics Hot Spots Risk Assessment Guidelines: Technical support document for the derivation of noncancer reference exposure levels.

OEHHA, 2008b. Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries: Manganeses and Compounds Reference Exposure Levels.

Perry, C.S., Blanchette, A.D., Vivanco, S.N., Verwiel, A.H., Proctor, D.M., 2023. Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. Regul. Toxicol. Pharmacol. 145, 105518.

Roels, H., Ghyselen, P., Buchet, J.-P., Ceulemans, E., Lauwerys, R., 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br. J. Ind. Med. 49, 25.

Takser, L., Mergler, D., Hellier, G., Sahuquillo, J., Huel, G., 2003. Manganese, monoamine metabolite levels at birth, and child psychomotor development. Neurotoxicology 24, 667–674.

TCEQ, 2017. Development Support Document: Manganese and Inorganic Manganese Compounds.

TCEQ, 2015. TCEQ Guidelines to Develop Toxicity Factors.

Appendix A

Table 1. Copy of Table 3-6 from the TCEQ Guidelines to Develop Toxicity Factors (pg. 91), which is a comparison of UFs used by different organizations (TCEQ, 2015).

Uncertainty Factors	TCEQ	USEPA	ATSDR	OEHHA	FDA	ECETOC	Netherlands	Health Canada/ IPCS
Interspecies, UF_H	≤ 10	≤ 10	1, 3, or 10	≤ 100	10	2 – 7 (systemic effects) 1 (local effects)	3	10
Toxicokinetics, UF_{H-k}	3	3	--	1, 3, or 10	--	--	--	2.5
Toxicodynamics, UF_{H-d}	3	3	--	1, 3, or 10	--	--	--	4
Intraspecies, UF_A	≤ 10	≤ 10	1, 3, or 10	≤ 10	10	5	10	10
Toxicokinetics, UF_{A-k}	3	3	--	1, 2, or 3	--	--	--	2.5
Toxicodynamics, UF_{A-d}	3	3	--	1,2, or 3	--	--	--	4
Subchronic to chronic, UF_{Sub}	≤ 10*	≤ 10	1, 3, or 10	1, 3, or 10	10	2 (default) 1 (local effects)	1 to 10	1 to 100 for UF_{Sub}, UF_L, & UF_D
LOAEL to NOAEL, UF_L	2 – 3* (≤ mild) 6 *(mild/severe) 10* (severe)	≤ 10	3 (minimal effects) 10 (serious effects)	6 (mild effects) 10 (severe effects)	N/A	3 (default) ± 3 (depends on severity)	1 to 10	See above
Incomplete database, UF_D	≤ 10* = database deficiency and key study quality, including child/adult differences	≤ 10	N/A	1 or 3	N/A	1 (high confidence level) 1-2 (medium) < 2 (low)	N/A	See above
Modifying factor, UF_M	N/A	≤ 10 (discontinued)	1 to 10	N/A	N/A	1 to 10	1 to 10	1 to 10

*For TCEQ, since the UF_{Sub}, UF_L, and UF_D are not based on geometric half values, the actual value for UF_{Sub}, UF_L, and UF_D will be used to form the final product of all UFs (i.e., use of a 3 will count as a 3 and not as $10^{0.5}$).