State of Oregon
DEQ Department of Environmental Quality

Memorandum

To: Ali Mirzakhalili, DEQ Air Quality Administrator

CC: JR Giska, DEQ Cleaner Air Oregon Program Manager

From: Cleaner Air Oregon Toxicology Team

- Holly Dixon, Oregon Health Authority (OHA) Public Health Toxicologist
- David Farrer, OHA Public Health Toxicologist
- Mike Poulsen, DEQ Toxicologist
- Susan MacMillan, DEQ Air Toxics Science & Policy Analyst

Date: July 26, 2024

Subject: DEQ Toxicity Reference Value (TRV) Proposal for 24-hour Acute Inhalation Exposure to Manganese

1. Key Takeaway

DEQ proposes that the DEQ toxicity reference value (TRV) for 24-hour acute inhalation exposure to manganese should be changed from 0.3 µg/m^3 to 1.3 µg/m^3.

2. Background Information

2.1. Current DEQ TRV

DEQ's existing TRV for 24-hour acute inhalation exposure to manganese is 0.3 µg/m^3. Hereafter, the acute manganese TRV is referred to as the "acute TRV". A TRV is the concentration of a toxic air contaminant below which it is unlikely to cause health problems when inhaled. The existing acute TRV is based on a chronic exposure TRV from CalEPA's Office of Environmental Health and Hazard Assessment (OEHHA). The existing TRV is based on a study that reported neurotoxicity in workers exposed to manganese for an average of 5.3 years and up to 17 years (Roels et al., 1992). DEQ would prefer to derive an acute TRV from a study with an acute exposure duration. In cases where chronic exposure studies are used to derive an acute exposure TRV, DEQ stated in the TRV update fact sheet that DEQ and Oregon Health Authority (OHA) would prioritize finding alternative TRVs that are based on studies with acute exposure periods during the TRV review.

2.2. Current TRV Review and Manganese Petition

DEQ and OHA are currently reviewing the inhalation 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 acute manganese TRV (Bridgewater Group, 2022). The 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 reference value (ReV) developed by the Texas Commission on Environmental Quality (TCEQ, 2017). While the TRV proposed by Bridgewater Group is equivalent to the TCEQ TRV, the Bridgewater Group petition proposed a different set of uncertainty factors (UFs) in its derivation than the ones used by TCEQ.

Staff at ToxStrategies 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.". The Perry et al. manuscript states that the work was supported by Gunderson LLC, of Portland, OR and Cascade Steel Rolling Mills, Inc., of McMinnville, OR. Similar to the Bridgewater Group petition, the acute TRV proposed by Perry et al. for manganese is equivalent to the TCEQ TRV; however, Perry et al. proposes a different set of uncertainty factors compared to TCEQ and the Bridgewater Group petition.

The similarities and differences between the Bridgewater Group petition, TCEQ, and Perry et al. are discussed in detail in this DEQ framing document that was written by DEQ and OHA to prepare the Air Toxics Science Advisory Committee (ATSAC) for a discussion on potentially changing DEQ's acute TRV. For more information about the purpose of ATSAC and background of ATSAC members, refer to this DEQ website.

2.3. ATSAC Member Feedback on the Petition

DEQ and a third-party meeting facilitator, Kearns & West, held an ATSAC meeting on **April 3, 2024**, to gather feedback from ATSAC members on the Bridgewater Group petition. ATSAC members were asked to read the petition, the Perry et al. manuscript, and DEQ's framing document, and also prepare answers to DEQ's discussion questions in advance of the meeting. ToxStrategies as well as DEQ and OHA staff gave presentations during the meeting. During the meeting, ATSAC members discussed each component of deriving an acute TRV given the key studies used by the Bridgewater Group petition, TCEQ, and Perry et al. DEQ did not develop an acute TRV proposal in advance of the ATSAC meeting. ATSAC member feedback from the meeting was used to inform the TRV proposal that is in this memorandum. **ATSAC meeting minutes are available here and a video recording is available here.**

Following the April 3, 2024 ATSAC meeting, Bridgewater Group, ToxStrategies, and TCEQ provided additional documents and information which were shared with ATSAC as follows:

- **April 8, 2024**: ToxStrategies sent DEQ additional information related to some of the ATSAC questions asked during the April 3 meeting (document linked here).
- **April 9, 2024**: Joseph Haney in the Toxicology Division at TCEQ emailed OHA additional information about exposure duration adjustments (email linked here).
- **April 12, 2024**: DEQ shared the additional information sent by ToxStrategies and TCEQ on April 8 and April 9 with ATSAC and asked ATSAC three follow-up questions via email.

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The email DEQ sent to ATSAC as well as the compiled ATSAC feedback is available in this document.

- **May 7, 2024**: Bridgewater Group sent DEQ an additional report from ToxStrategies regarding the time adjustment factor to the acute TRV (email and report linked here).
- **May 15, 2024**: DEQ shared the additional information sent by Bridgewater Group on May 7 with ATSAC and asked if ATSAC opinions had changed due to the new information. The email DEQ sent to ATSAC as well as compiled ATSAC feedback is available in this email thread. DEQ also compiled ATSAC members' TRV derivation worksheets in this document and sent to ATSAC. To date, no ATSAC members have requested any changes to their TRV derivation worksheets.

3. TRV Proposal

The Cleaner Air Oregon toxicology team considered the acute TRV information received from the Bridgewater Group and ATSAC. Hereafter, the Cleaner Air Oregon toxicology team will be referred to as "DEQ". DEQ proposes the following derivation for DEQ's 24-hour acute inhalation exposure manganese TRV (Table 1).

Table 1. DEQ's proposed derivation of the 24-hour acute manganese TRV.

Parameter	Summary
Key Studies	Dorman et al. (2005) and Erikson et al. (2008)
Study Population	Male Rhesus Monkeys (20-24 months)
Exposure Method	Inhalation of $MnSO_4$
Exposure Continuity	6 hours/day, 5 days/week
Exposure Duration	15 exposure days
Critical Effects	Dorman et al. 2005 • Respiratory system • Inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation) Erikson et al. 2008 • Nervous system • Biochemical markers of oxidative stress in the brain (decreased glutathione levels and reversible increased glutamine synthetase protein with decreased gene expression)
Point of Departure (POD)	1.5 mg/m^3; lowest observed adverse effect level (LOAEL)
Time Adjusted Exposure	0.375 mg/m^3 [=1.5 mg/m^3 x (6 hr/24 hr)]
Human Equivalent Concentration	0.375 mg/m^3
Interspecies Uncertainty Factor (UF_A)	3
Intraspecies Uncertainty Factor (UF_H)	10
LOAEL Uncertainty Factor (UF_L)	3
Subchronic Uncertainty Factor (UF_S)	NA

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Parameter	Summary
Database Uncertainty Factor (UF_D)	3
Total Uncertainty Factor	300 (=3x10x3x3)
24-hour Acute Manganese TRV	**1.3 µg/m^3 (rounded from 1.25 µg/m^3)**

3.1. Key Studies and Point of Departure (POD)

DEQ proposes to use the same two key studies (Dorman et al. 2005 and Erikson et al. 2008) that are used in Perry et al. Both studies have the same POD, a lowest observed adverse effect level (LOAEL) of 1.5 µg/m^3. DEQ agrees with the Bridgewater Group that these two key studies are a good resource for developing a new DEQ acute TRV for three primary reasons:

1. The exposure durations in these studies are much closer to DEQ's definition of acute exposure than the key study used in DEQ's current acute TRV. The average exposure time is 5.3 years in Roels et al. (1992), the key study currently being used by DEQ for an acute TRV.
2. The study populations are monkeys rather than other animal models (such as rodents) that are less similar to humans.
3. The manganese exposures and particle size are well characterized.

DEQ acknowledges that Dorman et al. 2005 and Erikson et al. 2008 also have limitations. Examples of limitations include:

- Both key studies are small, with around 4-6 monkeys per exposure group.
- Both key studies looked at limited exposure concentrations and endpoints.
- As described further in Section 3.8 below, DEQ's authoritative sources (the Agency for Toxic Substances and Disease Registry (ATSDR) and OEHHA) decided not to derive an acute toxicity value after a comprehensive review of all available toxicity information. The Dorman et al. 2005 study was available during ATSDR's and OEHHA's reviews and it is cited in both of those organization's derivation documents.

ATSAC members provided feedback on deriving a proposed DEQ acute TRV using both Dorman et al. 2005 and Erikson et al. 2008 (e.g., compiled ATSAC worksheets). Generally, ATSAC members were supportive of using Dorman et al. 2005 and Erikson et al. 2008 as the key studies for deriving a new DEQ acute TRV. ATSAC members also highlighted study limitations. For example, John Budroe stated that "Dorman 2005 and Erikson 2008 are not especially good studies; these studies have a freestanding LOAEL with no controls" (DEQ, 2024a). In addition, here is an excerpt from the meeting minutes describing ATSAC member Daisy Dong's comments:

> "Daisy agreed with combining both studies (Dorman et al. 2005 and Erikson et al. 2008). Daisy notes that a major limitation of these studies is that they have one dose. She said that if DEQ has to come up with an acute TRV, and if the other options are to not have an acute TRV at all or to adapt a chronic TRV, she prefers using the two critical studies in Table 1 (Dorman et al. 2005 and Erikson et al. 2008). The primate studies are preferable over the rat studies due to their greater relevance to humans. The combination of the two

> critical studies also gives us more information for a regulatory toxicity value than only gene expression or protein level data." (DEQ, 2024a).

Overall, DEQ proposes using both Dorman et al. 2005 and Erikson et al. 2008 to derive a DEQ acute TRV rather than DEQ's current approach of using a key study with a chronic exposure duration.

3.2. Time Adjustment

DEQ proposes to apply an exposure time adjustment since the monkeys in the key studies were exposed 6 hours/day, 5 days/week for 15 exposure days, whereas the 24-hour TRV is designed to protect against a daily exposure.

DEQ proposes to multiply the POD concentration by 6 hours/24 hours to adjust the intermittent exposure regimen in the key studies to a continuous 24-hour TRV:

$$\begin{aligned} \text{24-hour Time Adjusted POD} &= \text{POD} \times \frac{6 \text{ hours}}{24 \text{ hours}} \\ &= 1.5 \text{ mg/m}^3 \times 0.25 \\ &= 0.375 \text{ mg/m}^3 \end{aligned} \qquad \text{(Eq. 1)}$$

The Bridgewater Group petition, TCEQ, and Perry et al. did not include a time adjustment in the derivation of their acute TRVs. In contrast, all ATSAC members supported a time adjustment to account for adjusting the exposure duration from 6 hours/day in the key studies to a 24-hour TRV. After additional information was provided by Bridgewater Group, ToxStrategies and TCEQ on this issue, no ATSAC members requested any changes to their prior recommendation.

Two ATSAC members responded to DEQ after DEQ sent ATSAC the May 7 ToxStrategies report on the time adjustment. Both ATSAC members continued to support the addition of the time adjustment and DEQ agrees with their reasoning. For example, ATSAC member Daisy Dong stated:

> "The additional information [from ToxStrategies] only addressed the pharmacokinetic (PK) difference but not the pharmacodynamic (PD) difference between the continuous 24h exposure and the 6hr/d, 5d/wk for 3 weeks exposure. As I commented earlier, only when both PK **AND** PD indicate no differences between these two exposure scenarios, then it is ok not to do time adjustment. Therefore, my opinion stays same as before." – Source: ATSAC Email Responses to Petitioner Supplemental Information, May 22, 2024

Pharmacokinetics (PK) and toxicokinetics (TK) are terms that are used interchangeably in many situations, as in the case of the ATSAC quote above and other places in this memorandum. This is also the case for pharmacodynamics (PD) and toxicodynamics (TD). Briefly, TK describes toxic contaminant uptake, internal distribution, biotransformation, and elimination in an organism; i.e., what an organism does with a toxic contaminant like manganese (Ashauer & Escher, 2010). TD

describes what the toxic contaminant does to the organism, which can include information on the time course of toxic action at the target site, physiological impairment of the organism, and emergence of toxic effects such as mortality (Ashauer & Escher, 2010). TK is termed PK in pharmacology and TD is termed PD in pharmacology; these terms in pharmacology reference a therapeutic drug instead of a toxic contaminant.

ATSAC member John Stanek also brought up an observation that while TCEQ's 24-hour toxicity value does not use a time adjustment, TCEQ's 1-hour toxicity value based on the same key study (Dorman et al. 2005) uses a time adjustment based on Haber's rule as modified by ten Berge et al.:

> "I found it interesting as cited in Table 1 of Perry that TCEQ applied a modified (ten Berge) Cxt to calculate a 1-hr value (using the same Dorman study LOAEL of 1.5 mg/m3 for respiratory effects). However, they determined not to apply it to extrapolate to 24-hrs – this appears methodologically inconsistent to me and is the one of the bases for this issue." – Source: ATSAC Email Responses to Petitioner Supplemental Information, May 22, 2024

TCEQ's *Guidelines to Develop Toxicity Factors* covers TCEQ's default approaches for time adjustments (section 4.6.2.4.1.2):

> "When a chemical's MOA is poorly characterized, the C exponent, "n" (see Section 3.8 regarding Haber's rule, $C^n \times T = K$), is set equal to a default value of 1, which is considered to be conservative when performing a duration adjustment from a shorter exposure duration to a longer one." (TCEQ, 2015).

TCEQ used n=3 in the modified (ten Berge) Haber's rule equation above for their 1-hour toxicity value based off Dorman et al. 2005. The n=3 is TCEQ's default assumption when going from a longer exposure period to shorter exposure toxicity value. Here, DEQ is taking a shorter exposure period from Dorman et al. 2005 and Erikson et al. 2008 (6 hours/day) and applying that exposure to a longer 24-hour TRV. With the information available in the key studies, DEQ agrees with a n=1 for Haber's rule, which is equivalent to the time adjusted POD proposed in Eq. 1.

3.3. Adjustment from Animal-to-Human Exposure

DEQ proposes to use a regional deposited dose ratio (RDDR) of 1 due to the similarities in lung anatomy between rhesus monkeys and humans. For example, Perry et al. states:

> "Dorman et al. (2005) discussed the similarities of monkey and human respiratory-tract anatomy, stating that, based on the Asgharian et al. (1995) model, a particle size of 1.5 μm (near the 1.72- to 2.12-μm range used by Dorman et al. (2005)) predicted approximately equal pulmonary deposition efficiency of 35% in both humans and rhesus monkeys. Therefore, no dosimetric adjustment is required when using these data to assess exposures in humans. Further, Campbell et al. (2023) demonstrated that the rate

> constants for binding and cellular uptake established in monkeys are applicable to humans." (2023).

To derive the Human Equivalent Concentration POD in Table 1, the Time Adjusted POD was multiplied by the RDDR of 1:

$$\begin{aligned} \text{24-hour Human Equivalent Concentration} &= \text{Time Adjusted POD} \times \text{RDDR} \\ &= 0.375\ \text{mg/m}^3 \times 1 \\ &= 0.375\ \text{mg/m}^3 \end{aligned} \qquad \text{(Eq. 2)}$$

No ATSAC member suggested a different adjustment for animal-to-human exposure. Compiled ATSAC feedback indicates that all ATSAC members agreed that no additional adjustment is needed to calculate the Human Equivalent Concentration.

3.4. Interspecies Uncertainty Factor (UF_A)

A UF_A is used to account for the uncertainty in extrapolating laboratory animal data to humans (U.S. EPA, 1994). The study population in the two key studies are non-human primates (rhesus monkeys), so DEQ selected a **UF_A of 3**. If the key studies had been human studies, DEQ would have selected a UF_A of 1. The respiratory and nervous systems are very similar between humans and rhesus monkeys, which is why DEQ chose a UF_A of 3 instead of 10. The similarities in the respiratory system are noted in Section 3.3 above. The similarities in the nervous system are noted in Perry et al.:

> "We consider monkeys to be a preferable human model to rats, due to their similarities to humans in Mn [manganese] brain accumulation distribution patterns, neurological signs, and nose/brain anatomy and physiology (Burton and Guilarte, 2009; Newland, 1999; Dorman et al., 2006). Further, unlike rodents, nonhuman primates largely replicate the neurotoxic effects of Mn observed in humans (Dorman, 2023)" (2023).

Compiled ATSAC feedback indicates that all ATSAC members are in support of a UF_A of 3 when using Dorman et al. 2005 and Erikson et al. 2008 as the key studies.

3.5. Intraspecies Uncertainty Factor (UF_H)

A UF_H is used to account for the variation in sensitivity among members of the human population (U.S. EPA, 1994). DEQ proposes a **UF_H of 10** to address DEQ's concern that prenatal and young children may be more susceptible to manganese exposure due to toxicodynamic differences between developing children and adults. OEHHA's comprehensive manganese report highlights eight reasons why children may be more susceptible to manganese toxicity than adults (2008). Here are three examples from OEHHA's report:

1. "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."

2. "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)."
3. "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."

Five of the six ATSAC members recommended a UF_H of 10 and one recommended a UF_H of 30 (included an additional subfactor of 3 to adjust for residual pharmacokinetic differences they did not think were accounted for by the petitioner's PBPK modeling). For context, UFs are generally 3- to 10-fold factors (U.S. EPA, 1994). OEHHA toxicity values can have UF_Hs of up to 100, but 10 is usually the maximum UF_H for DEQ's other authoritative sources (EPA and ATSDR). A comparison of UFs used by different organizations is in Appendix A of DEQ's Manganese Framing Document (DEQ, 2024b).

3.6. LOAEL to NOAEL Uncertainty Factor (UF_L)

A UF_L is used to account for the uncertainty in using LOAEL data rather than no observed adverse effect level (NOAEL) data for the POD (U.S. EPA, 1994). DEQ proposes a **UF_L of 3** because, although a NOAEL was not available, most critical effects in the key studies were reported to be mild and reversible (Table 1). For example, Dorman et al. and Erikson et al. state:

- "High-dose subchronic manganese sulfate inhalation is associated with increased lung manganese concentrations, mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue. Bronchiolitis and alveolar duct inflammatory changes were absent 45 days post-exposure, suggesting that these lesions are reversible upon cessation of subchronic high-dose manganese exposure. These small airway changes occurred in the absence of observable clinical signs." (Dorman et al., 2005).
- "Overall, the nonhuman primate brain responds to airborne Mn in a heterogeneous manner and most alterations in these biomarkers of neurotoxicity are reversible upon cessation of Mn exposure." (Erikson et al., 2008).

DEQ's proposal of a UF_L of 3 is in line with two of DEQ's authoritative sources. For example, ATSDR uses a UF_L of 3 when the LOAEL has minimal effects and OEHHA uses a UF_L of 6 when the LOAEL has mild effects (DEQ, 2024b). A UF_L of 1 is not warranted because a NOAEL is not available in the key studies.

Perry et al. and three ATSAC members were in support of a UF_L of 10. ATSAC statements included:

- "It is worth to mention that a LOAEL to NOAEL of 10 is not overly conservative given that the critical effects include neurotoxicity and many brain neurotoxicity biomarkers did

change at the LOAEL in monkeys." – ATSAC member Daisy Dong (DEQ and ATSAC Email Communication 4-26-2024)

- "A full UF for LOAEL is likely warranted as there is not a defined NOAEL under similar exposure conditions (without making a few assumptions)." – ATSAC member John Stanek (Compiled ATSAC Manganese TRV Worksheets)

The other three ATSAC members had similar opinions and suggested UF_Ls of 2, 3, and 6. ATSAC member Susan Tilton stated, "I recommend an extrapolation of 2-fold since the observed pulmonary pathology was characterized as mild/minor and reversible." ATSAC member John Budroe picked a 6 because the LOAEL is a mild effect, and this qualifies as a UF_L of 6 following OEHHA guidance. Another ATSAC member did not propose a final UF_L, but stated he wondered if more work could be done to further explore reducing the UF_L.

Overall, DEQ did not think a UF_L of 10 was warranted given that most of the critical effects for the LOAEL were characterized as mild and reversible. DEQ acknowledges that not all the neurotoxicity biomarkers in Erickson et al. were observed to be reversible during the timeframe of the study. DEQ looked at the totality of information available in both key studies to decide to choose a reduced UF_L. In addition, while DEQ contemplated each UF individually, DEQ did consider the interplay between the UF_L and UF_D and thinks that these UFs are closely related. The product of both the UF_L and UF_D was similar across all ATSAC members (refer to section 3.9; i.e., ATSAC members that selected a UF_L of 10 then selected a UF_D of 1 and ATSAC members that selected a reduced UF_L then selected a UF_D of 3). With both the UF_L and UF_D, DEQ is building in a safety buffer to protect against the potential of neurodevelopmental effects in sensitive populations given limited toxicological information.

3.7. Subchronic Uncertainty Factor (UF_S)

A UF_S is not applicable. A UF_S is only for extrapolating subchronic exposure durations to chronic TRVs, and not for extrapolating subchronic exposure durations to acute TRVs.

3.8. Database Uncertainty Factor (UF_D)

A UF_D is used to account for the inability of a single study (or two) to adequately address all possible adverse human health outcomes (U.S. EPA, 1994). DEQ proposes a **UF_D of 3** to address DEQ's concern about the lack of studies on the impact of manganese on the developing nervous system.

Other organizations that have done comprehensive reviews on the available manganese toxicology database have commented on the lack of information.

ATSDR. As ATSAC member John Budroe pointed out, ATSDR's 2012 Manganese Toxicological Profile stated that the available data on the toxicity of inhaled manganese was considered insufficient for deriving an acute or intermediate duration inhalation toxicity value (ATSDR, 2012; DEQ, 2024a). ATSDR's toxicological profile also has a section on physiologically based pharmacokinetic (PBPK) and pharmacodynamic (PD) models (section 3.4.5 of ATSDR's Tox Profile). However, ATSDR does not use the PBPK and PBPD models to inform an acute or

intermediate duration toxicity value. David Dorman, the first author of one of the key studies in the TRV proposal in this memorandum, was one of three peer reviewers of the ATSDR Manganese Toxicological Profile, which implies he had the opportunity to comment on and review ATSDR's decision to not derive toxicity values for acute or intermediate duration inhalation exposures.

OEHHA. OEHHA did not develop an acute exposure TRV for manganese in their 2008 report because "the database is insufficient" (OEHHA, 2008). The Dorman et al. 2005 study was available during OEHHA's review and is referenced in the report. OEHHA provided information on why the potential for developmental neurological issues from manganese is a concern (OEHHA, 2008). OEHHA stated 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 (OEHHA, 2008). 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 (attention, nonverbal memory, and hand skills) measured at three years of age (OEHHA, 2008; 2003).

TCEQ. TCEQ used the Dorman et al. 2005 study to derive an acute TRV. They used a UF_D of 6 in their derivation. 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)" (2017). TCEQ also comments, "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" (2017).

Three ATSAC members suggested a UF_D of 3, mentioning this UF is needed to reflect the lack of neurobehavioral development data. Three ATSAC members suggested a UF_D of 1 and expressed confidence in the Bridgewater Group's PBPK modeling. ATSAC member Daisy Dong recommended a UF_D of 1 and stated that these manganese PBPK models, compared to other chemicals, are actually quite good and included many different variables such as diet contribution and different manganese forms (DEQ, 2024a).

Overall, DEQ did not think that a UF_D of 1 was adequate given the information from ATSDR, OEHHA, and TCEQ on the lack of a complete database. DEQ also did not think a UF_D of 10 was warranted given that no ATSAC members suggested a UF_D of 10 and half of the ATSAC members suggested a UF_D of 1. DEQ chose a UF_D of 3 for the final proposal, which aligned with the other half of the ATSAC members.

3.9. Total UF

The proposed UFs differed between ATSAC members and organizations (Figure 1). A range of UF proposals was expected; uncertainty is inherent in deriving TRVs and strategies for quantifying uncertainty differ between toxicologists as well as organizations that set TRVs. However, even though there was a range of UF proposals, trends emerged as mentioned in the subsections

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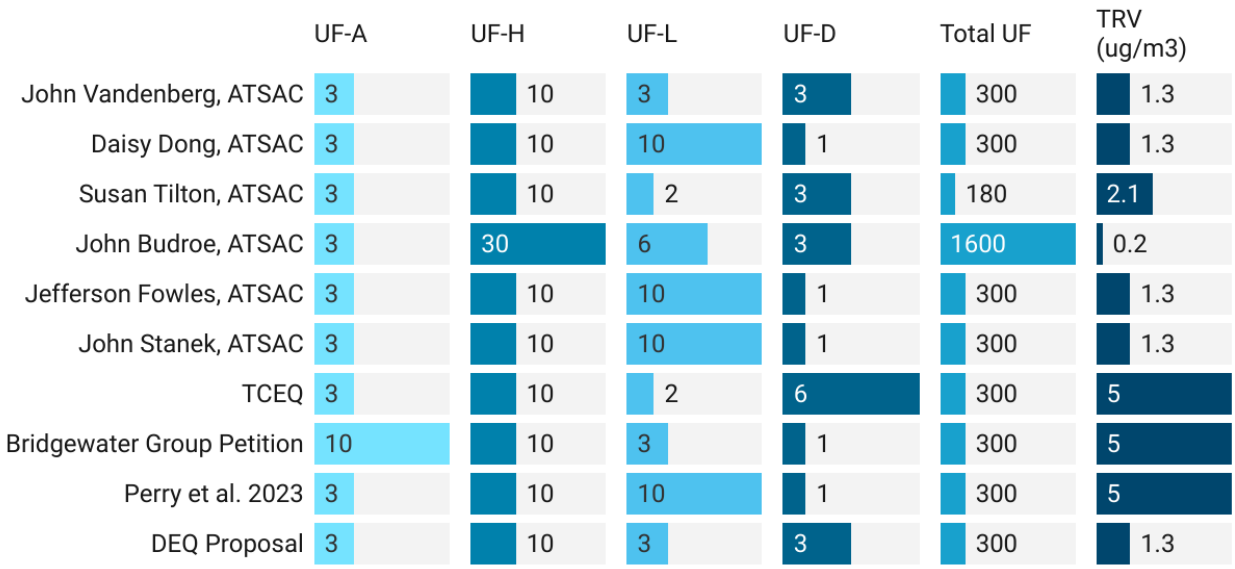
above and seen in Figure 1. DEQ's proposal incorporates these trends and reflects DEQ's health protective approach to scientific uncertainty.

Figure 1. Comparison of the proposed UFs and TRV between the six ATSAC members, TCEQ, the Bridgewater Group petition, Perry et al., and DEQ. The size of each bar is scaled to the range for each column.



Source: Oregon DEQ 2024 • Created with Datawrapper

DEQ proposes a total UF of 300 as calculated below:

$$\begin{aligned} \text{Total UF} &= \text{UF}_\text{A} \times \text{UF}_\text{H} \times \text{UF}_\text{L} \times \text{UF}_\text{D} \\ &= 3 \times 10 \times 3 \times 3 \\ &= 300 \text{ (rounded to one significant figure)} \end{aligned} \quad \text{(Eq. 3)}$$

Four of the six ATSAC members suggested a total UF of 300, which is equivalent to the DEQ proposal. ATSAC members suggested total UFs ranging from 180 to 1600 (Figure 1).

3.10. TRV Proposal and Conclusion

DEQ proposes that the DEQ TRV for 24-hour acute inhalation exposure to manganese should be 1.3 µg/m^3 (rounded from the calculated value of 1.25 µg/m^3):

$$\begin{aligned} \text{Proposed DEQ 24} - \text{Hour Acute TRV} &= \text{Human Equivalent Concentration POD} \div \text{Total UF} \\ &= 0.375 \text{ mg/m}^3 \div 300 \\ &= 0.00125 \text{ mg/m}^3 \\ &= 1.3 \text{ µg/m}^3 \text{ (rounded to two significant figures)} \end{aligned} \quad \text{(Eq. 4)}$$

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DEQ's priority when deriving this TRV was to make sure that the TRV protects the health of vulnerable populations, such as children during critical developmental windows. DEQ's proposal is also equivalent to the TRV proposals from four of the six ATSAC members (Table 2). ATSAC member TRV proposals ranged from 0.2 to 1.3 µg/m^3 (Table 2).

Table 2. Comparison of proposed derivation information between TCEQ, the Bridgewater Group petition, Perry et al., ATSAC members, and DEQ for a 24-hour acute manganese TRV.

	Time Adjust.?	Human Equiv. Conc. Adjust.?	Uncertainty Factor (UF)						TRV (µg/m^3)
			UF_A Inter-species	UF_H Intra-species	UF_L LOAEL	UF_S Sub-chronic	UF_D Data base	Total UF	
TCEQ	No	No	3	10	2	NA	6	300*	5.0
Bridgewater Group Petition	No	No	10	10	3	NA	1	300	5.0
Perry et al. 2023	No	No	3	10	10	NA	1	300	5.0
Range from ATSAC Members	Yes	No	3	10 to 30	2 to 10	NA	1 to 3	180 to 1600	0.2 to 1.3
DEQ Proposal	**Yes**	**No**	**3**	**10**	**3**	**NA**	**3**	**300**	**1.3**

*While the total UF is equivalent to 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.

To put this acute TRV in context of DEQ's other TRV for manganese inhalation exposure, DEQ's 2018 chronic noncancer TRV for manganese is 0.09 µg/m^3 (OEHHA value adopted by a previous ATSAC). DEQ is not proposing to change this chronic noncancer TRV in the current TRV review. There is no cancer TRV available for manganese.

References

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800-452-4011 | TTY: 711 | deqinfo@deq.oregon.gov