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SUBJECT: Further Clarification Following the ODEQ ATSAC Meeting on April 3, 2024

Dear Ms. Goeckner:

We wanted to thank you for the opportunity to present to the Air Toxics Science Advisory Committee (ATSAC) on April 3, 2024. After our presentation, we continued to listen to the ATSAC's discussion and wish to clarify points relevant to some of the questions asked, based on our work on the toxicology of manganese over the last several years.

Oregon Department of Environmental Quality's (ODEQ's) current 24-hour acute manganese toxicity reference value (TRV) of 0.3 µg/m^3 does not reflect the best available science, and it vastly over-estimates potential risk from 24-hour exposures to manganese in ambient air.

In our opinion, a comprehensive understanding of the current science amply supports an acute TRV of 5 µg/m^3. The information supporting that value includes the Perry et al. (2023) publication, our presentation at the Society of Environmental Chemistry and Toxicology (SETAC) meeting (Perry et al., 2022), and the recent poster presented at Society of Toxicology (SOT) meeting (Perry et al., 2024).

We appreciate ATSAC's consideration of the proposed acute TRV of 5 µg/m^3, including whether and how uncertainty factors or exposure adjustment factors apply to that value. Overall, we believe that the physiologically based pharmacokinetic (PBPK) modeling results reduce uncertainty in the derived TRV and, accordingly, reduce the need for conservative uncertainty factors or exposure adjustment factors. Specifically, conservative and appropriate uncertainty factors were already used to develop the proposed acute TRV, and the PBPK modeling results verified that acute exposures at the proposed TRV did not significantly increase tissue manganese levels above background levels maintained by homeostasis. In developing the proposed TRV, we also looked at benchmarks in the literature for air and tissue concentrations and found that an acute TRV of 5 µg/m^3 is protective for respiratory and neurological effects. The best available science supports the proposed TRV value without application of additional uncertainty or exposure adjustment.

In support of ATSAC's further consideration of that position, after reviewing some general information about manganese that is critical to evaluating dose response and developing an acute TRV, below we provide clarifying information about the following two aspects of the ATSAC's discussion regarding the proposed TRV value:

- Whether the point of departure (POD) should be adjusted for duration of exposure, and
- Selection of appropriate uncertainty factors.

Manganese is an Essential Nutrient

As discussed, the TRV for manganese should consider that manganese is an essential nutrient and appropriate uncertainty factors may vary as compared to those used for chemicals and metals which are not essential.

- Manganese demonstrates a U-shaped dose-response curve. We naturally carry a necessary amount of Mn in our bodies from background exposures in diet, water, and ambient air. Too little or too much manganese can create adverse effects.
- For manganese and other essential nutrients, the unnecessary compounding of uncertainty factors applied to study data can result in unnecessarily low toxicity criteria, where exposures are well below background conditions.
- A highly vetted human PBPK model for manganese has been used to verify that the proposed acute TRV is protective.

Adjusting the Point of Departure for Study Duration

As ATSAC discussed, we used the LOAEL of 1.5 mg/m^3 as the point of departure without an adjustment for exposure duration to develop the acute TRV.

Perry et al. (2023) is a peer-reviewed publication. While we received a substantial number of comments from the reviewers, none questioned the approach of not adjusting based on exposure time from the subacute points of departure (PODs). The Perry et al. (2022) presentation and Perry et al. (2024) poster were well-received at scientific meetings. Additionally, the Texas Commission on Environmental Quality (TCEQ)'s 2015 Toxicity Factor Guidance underwent peer review coordinated by Toxicology Excellence for Risk Assessment (TERA). Additionally, the specific approach for 24-hour exposures (TCEQ, 2014) and the Manganese Development Support Document (TCEQ, 2017) underwent public comment. In all cases, the rationale for not time-adjusting the subacute POD was not questioned.

The Dorman et al. (2005) and Erikson et al. (2008) studies in question included exposure periods totaling 90 hours over three weeks and are conservative for developing a 24-hour acute TRV. During their discussion, several ATSAC members considered applying an exposure adjustment factor of 4 to the POD from the Dorman et al. (2005) and Erikson et al. (2008) studies, because exposure in the studies occurred for 6 hours out of 24 hours in

a day rather than continuously for 24 hours. Importantly, the study exposure period was not for a single, 6-hour day, but extended for a total of 90 hours (30 hours per week for a 3-week period).

Moreover, Table 2 of Dorman et al. (2005) presents manganese concentrations in the lung following 1.5 mg/m^3 at 15 days (90 hours), 33 days (198 hours) and 65 days (390 hours) of total exposure. Mn concentrations were essentially equal at each time point, ranging from 0.33 to 0.39 μg/g tissue, demonstrating that manganese tissue concentrations in the target tissue of the lung had reached steady state by the 90 hour time point. As such, we would not expect lung tissue levels to be higher following a single 24 hour exposure than that for 6 hours per day, for 15 days (or a total of 90 exposure hours), which is the exposure at the POD.

USEPA (1994) recognized the uncertainty in assuming a temporal relationship of toxicity and duration adjustment. According to EPA: "The rationale for this linear prorate adjustment is that the resultant human exposure concentration should be the concentration (C) x time (T) equivalent of the experimental animal exposure level. This adjustment is weakly founded because steady-state conditions may not be reached in laboratory animals for some chemicals and intermittent regimens (applicable to extrapolation from shorter to longer-term exposures)." EPA's analysis applies to manganese and the POD because as described above, lung tissue had reached steady state within the exposure period used to define the POD. In short, given that manganese for 6 hours per day, for 15 days, had reached steady state concentrations in the lung, it is not reasonable to include additional time adjustment to account for 6 hours per day of exposure as compared to 24 hours/day.

USEPA has also affirmed the use of PBPK modeling as the first and best means of extrapolating one dose-duration scenario to another. In its "Review of the Reference Dose and Reference Concentration Guidance Process" (2002), USEPA recommends that "the optimal approach for extrapolating from one dose-duration response situation to another is the use of a physiologically based pharmacokinetic model (PBPK) model." Our PBPK model considered two scenarios: monthly 24-hour exposures for a lifetime and a 3-week continuous exposure period consistent with the TRV and the Short-term Guideline Concentration. In neither case were manganese concentrations in the brain, liver, and blood significantly greater than background levels. The results of the PBPK model for manganese support that no additional exposure adjustment factor is necessary to protect acute exposures.

The decision to use the lowest-observed-adverse-effect level (LOAEL) without adjustment in Perry et al. (2023) also considered TCEQ's rationale derived from its "Guidelines to Develop Toxicity Factors" (2015). TCEQ identifies that subacute toxicity studies (i.e., repeated or continuous exposure to a chemical greater than one day to one month or less) may be of greatest value for developing 24-hour acute guideline values. The Dorman et al. (2005) and Erikson et al. (2008) studies are both subacute toxicity studies. TCEQ guidance recommends that "if it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-hour

POD without adjustment." This is the approach adopted by TCEQ for manganese. The unique properties of manganese were recognized by TCEQ when it used the subacute LOAEL without adjustment because:

> "accumulation of manganese in the lung predominated over the 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)."

Uncertainty Factors

As discussed during the ATSAC meeting on April 3, 2024, there are three areas where a range of uncertainty factors (UFs) was considered in ODEQ's Framework Document (ODEQ, 2024). Consensus appeared to be reached for the other two UFs: intraspecies UF ($UF_H = 10$) and subchronic UF ($UF_S = 1$). The three factors are discussed below:

- Interspecies uncertainty (UF_A) – Options of 3 and 10 were considered although a factor of 3 was recommended in Perry et al. (2023), based on the primate study from which the LOAEL was derived. PBPK modeling supports very similar Mn toxicokinetics between monkeys and humans.
- LOAEL to NOAEL (UF_L) – Using a factor of 3 would have been appropriate for the mild effects observed in the study, but Perry et al. (2023) used 10 to also address some additional uncertainty with the study duration of 6 hours per day for 5 days per week for 3 weeks (90 hours), rather than 24 consecutive hours of exposure. As stated in Perry et al. (2023), the proposed acute TRV included "a 10-fold uncertainty factor to account for LOAEL-to-NOAEL extrapolation and the lack of data for a continuous 24-h exposure period (emphasis added)."
- Database (UF_D) – Options from 1 to 6 were considered. However, based on the results of the PBPK modeling, which captured early, sensitive lifestages (starting at birth), and benchmarks for exposure and tissue concentrations in the literature, a further database uncertainty factor is not necessary.

In combination, the overall UF recommended in Perry et al. (2023) was 300. However, if a less conservative UF_L of 3 is used, and a 4-fold time adjustment is applied, the resulting TRV would be essentially equivalent. The combined time adjustment and uncertainty factor would be 400, as compared to 300. However, we believe that no time adjustment is needed given that the POD was measured under steady state conditions in the lung.

Additional Lines of Evidence Supporting a 5 µg/m^3 Acute TRV

In Perry et al. (2023) and the SOT poster (Perry et al., 2024), additional lines of evidence were provided supporting the acute TRV of 5 µg/m^3.

- In a rat developmental drinking water study with Mn up to 4 mg/L, Oshiro et al. (2022) reported no cognitive impairment among offspring when combined with maternal stress.

- Epidemiologic studies in children have shown cognitive effects in children associated with elevated blood manganese, but the range of blood Mn levels associated with cognitive effects varies considerably (Bhang et al., 2013; Haynes et al., 2015). Blood Mn levels in the PBPK model were consistent with background.

The proposed acute guideline of 5 $\mu g/m^3$ is conservative relative to chronic inhalation values.

- Bailey et al. (2009) proposed 2 $\mu g/m^3$ to 7 $\mu g/m^3$ as chronic reference concentrations.

- Schroeter et al. (2011) and Gentry et al. (2017) predicted that homeostasis maintains Mn levels in the brain target tissue at airborne concentrations below 10 $\mu g/m^3$.

- Yoon et al. (2011) indicated that maternal and fetal blood and brain Mn levels were still within the normal range at airborne concentrations less than 10 $\mu g/m^3$.

Summary

Manganese is a well-studied essential nutrient with advanced PBPK modeling to support developing an acute TRV. It is paramount, in revising DEQ's existing acute TRV, to consider the weight of the evidence (including the significant new information from the PBPK model) rather than simply compiling default adjustment and uncertainty factors. The PBPK model is the tool EPA has identified for this purpose. In this instance, the PBPK model provides support that regardless of exposure duration adjustment and UFs, an acute TRV of 5 $\mu g/m^3$ is protective of public health as presented in our peer-reviewed paper, SOT poster, and SETAC presentation, and as recommended by TCEQ. If uncertainty factors become so high that the resulting value is similar to the ATSDR chronic Minimal Risk Level (MRL) (0.3 $\mu g/m^3$), then ODEQ should withdraw the current acute TRV and wait for additional information before deriving an acute TRV.

Sincerely,

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Attachment A - Response to Specific Comments at the ATSAC Meeting on April 3, 2024
Attachment B - References

ATTACHMENT A

Responses to Specific Comments at the ATSAC Meeting on April 3, 2024

Attachment A: Responses to Specific Comments at the ATSAC Meeting on April 3, 2024

We are providing responses to the following questions raised during the ATSAC's April 3, 2024 meeting discussion of ODEQ's 24-hour toxicity reference value (TRV) for manganese (Mn) in case they are useful for further deliberations.

1. **How were in utero exposures addressed in deriving the proposed 24-hour TRV?**

In utero exposure was addressed by multiple lines of evidence. While the PBPK modeling started at birth (0 years of age), there are pregnancy modeling results in the literature. Yoon et al., 2011 performed PBPK modeling for fetal and neonatal Mn exposures in humans. Their modeled results showed similar or lower internal Mn levels in the brains of fetuses/neonates relative to the adult/pregnant female at Mn air concentrations as high as 10 $\mu g/m^3$. Further, the Mn levels predicted in the fetus/neonate were within the normal range. In Perry et al., 2023 blood manganese concentrations in adult females were essentially consistent with background exposures at 5 $\mu g/m^3$, further supporting that in utero Mn exposures at the proposed TRV will be consistent with background. These results indicate acute exposures at 5 $\mu g/m^3$, would not result in increased Mn exposure to the fetus and thus not adversely impact fetal development.

2. **Why were the exposure scenarios chosen (24-hours once per month and continuously for 3 weeks)?**

Acute exposure scenarios were chosen to address potential operational conditions of emission sources. The continuous 24-hour exposure once per month scenario represents an occasional but repeated excursion to the TRV level, which would result in twelve 24-hour exposures per year. As described in Perry et al. 2023, the 3-week scenario was also assessed because the TRV is derived from the short-term guideline concentration (SGC), which is designed to be protective of exposures for 'a few weeks.' The most relevant exposure scenario for the 24-hour TRV is the 24-hour exposure which was conservatively assumed to occur monthly.

3. **At proposed acute TRV, what percent of total Mn dose is from inhalation vs. background?**

The results of the PBPK model predict tissue concentrations in the globus pallidus would be 3 percent higher than in concentrations at background exposure levels for a 3 to 10-year old exposed to manganese in air at 5 $\mu g/m^3$. Increases for other age groups were lower. These tissue concentrations account for homeostatic mechanisms regulating the concentrations of manganese in blood.

4. Are the key studies are based on a single dose?

The key studies supporting the proposed 24-hour TRV are based on a single exposure concentration of 1.5 mg/m^3, occurring for 6 hours per day, 5 days per week, for 15 days, for a total 90-hour exposure period. However, as discussed in Perry et al., 2023 and our April 8, 2024 letter, the same studies included multiple doses evaluated for longer-term exposures (65 days). This exposure period is not consistent with an acute TRV scenario. Our literature search did not identify any studies evaluating a single 24-hour exposure, and we believe the Point of Departure (POD) is conservative as the basis of a n acute TRV.

5. Were control animals used in key studies?

Control animals were used in the Dorman et al., 2005 and Erikson et al., 2008 studies. The animals were exposed to the same filtered air as the test monkeys for 65 days (corresponding to the longer term exposures in the studies) and did not have observed effects. The control animal results from Dorman et al., 2005 were presented in Table 3 of Perry et al., 2023, and the Erikson et al., 2008 control results are presented in the referenced paper.

6. Why are there short-term increases in tissue concentrations in graphical displays for the modeling results before exposure occurred?

The modeling involves a combination of models, developed for different age groups, and each model had parameters averaged over periods of time, which caused some peaks unrelated to exposure. From Perry et al., 2023 Figure 1, an excerpt of which was shown in the slides, the 3-week exposure graph has a small (<0.01 µg/g) increase in Mn concentrations in the globus pallidus followed by a larger increase related to exposure followed by a decrease over time. The two increases occur between 3.25 and 3.5 years of age. The first, small peak, which is also apparent for the background exposure scenario, is due to the tissue volume changing, as this is the near beginning of the child model, and it takes a bit of time to even out. The second peak is from the start of the 3-week exposure to 5 µg/m^3 Mn.

7. Were background exposures in key studies of primates comparable to background exposures in PBPK model?

Table 1 in Erikson, et al., 2008, presents several average tissue concentrations for the primates in the control group that can be compared to estimated tissue concentrations from the PBPK model for background exposures for 3 to 10 year old children, which are presented in Figure 3 of Perry et al., 2024. Table 1 below presents these results for tissues common to both sets of results, and shows that the results are comparable.

Table 1. Comparison of Erikson et al., 2008 tissue concentrations in control animals to predicted background tissue concentrations in humans from the PBPK modeling (μg/g)

Tissue	Control Group (Erikson et al., 2008)	Background from PBPK modeling (males 3 to 10 years old) (Perry et al., 2024)
Globus pallidus	0.48	0.54
Cerebellum	0.44	0.38
Blood	0.01	0.011

ATTACHMENT B

References

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