Holly Dixon

From: Travis Quarles <tquarles@bridgeh2o.com>
Sent: Tuesday, May 7, 2024 5:08 PM
To: GOECKNER Apollonia * DEQ
Cc: GISKA JR * DEQ; Holly Dixon
Subject: Re: ATSAC Meeting 3: Follow Up Manganese Questions
Attachments: Letter_additional PBPK modeling_2024-05-07.pdf

Follow Up Flag: Follow up
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Hi Apple,

Thanks for your April 15 email concerning the work DEQ, OHA and ATSAC are doing to review the acute manganese TRV value. We are grateful for your consideration of the report that ToxStrategies prepared as well as the peer-reviewed research discussed. The ToxStrategies report was submitted to you on April 8, 2024, following ATSAC's meeting earlier in the month, and sought to address issues that arose at the meeting. Today, we submit a single additional data point that assists in confirming ToxStrategies' prior research, and we hope that there is still time for your team to take it into consideration.

Since our last correspondence, ToxStrategies completed supplemental PBPK modeling that will be submitted for publication in *Regulatory Toxicology and Pharmacology*. That work was to further assess whether it is necessary to adjust the point of departure (POD) under consideration to account for the 6-hour per day exposure duration in the underlying animal studies.

ToxStrategies' most recent modeling has determined that there is essentially no difference between the PBPK-model predicted maximum manganese tissue concentrations for the exposure scenarios in the underlying studies (6-hours per day, 5-days per week, 3 weeks), as compared to a 24-hour (acute) exposure scenario.

ToxStrategies' latest work is presented in the attached letter report. The data confirms the prior conclusions that: (1) no time-adjustment to the POD is needed to derive a health-protective acute (24-hour) manganese TRV; and (2) the proposed TRV of 5 $\mu g/m^3$ is protective.

We understand that, at this time, DEQ is not seeking further information on the petition to change the acute manganese TRV. However, ToxStrategies' latest PBPK modeling data is available now and it reflects the latest science on this issue. Therefore, we submit it in time for it to be considered while agency and ATSAC review of the acute manganese TRV is underway, and before any future TRV rulemaking based on that review is initiated. We would appreciate your consideration of this one additional point of reference.

Please let me know if you have any follow-up questions.
Thank you,
Travis

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On Apr 15, 2024, at 3:54 PM, GOECKNER Apollonia * DEQ <Apollonia.GOECKNER@deq.oregon.gov> wrote:

Travis,

We wanted to provide you, and ToxStrategies, with the materials and email communication that we sent to ATSAC members as a follow-up from the materials you all provided based on the discussion at the ATSAC meeting regarding the Mn petition . Materials linked below (the document from ToxStrategies and the email from TCEQ) have also been posted to the ATSAC meeting page. We will provide any future responses from the ATSAC members to these materials on the ATSAC meeting page as well.

We will no longer be accepting further information on this petition from your team – please use the next opportunity for formal feedback that will occur during the TRV Rulemaking process to provide any additional resources, comments, or feedback.

Thank you all again for the excellent discussion.

Best,
Apple

Apollonia (Apple) Goeckner | **Program Coordinator**
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From: GOECKNER Apollonia * DEQ
Sent: Friday, April 12, 2024 11:10 AM
To: John Budroe <jdbudroe@gmail.com>; Dong, Qiaoxiang@CDPR <Qiaoxiang.Dong@cdpr.ca.gov>; Jeff Fowles <jfowles101@gmail.com>; Tilton, Susan C <susan.tilton@oregonstate.edu>; Stanek, John

<Stanek.John@epa.gov>; John Vandenberg, Ph.D. <john.vandenberg@duke.edu>
Cc: Holly Dixon <Holly.M.Dixon@oha.oregon.gov>; Farrer David G <DAVID.G.FARRER@oha.oregon.gov>; MACMILLAN Susan * DEQ <Susan.MACMILLAN@deq.oregon.gov>; GISKA JR * DEQ <JR.GISKA@deq.oregon.gov>
Subject: ATSAC Meeting 3: Follow Up Manganese Questions

Hi ATSAC Members,

Thank you all again for your participation and thoughtful feedback during the ATSAC meeting last week.

New Update: This week we received a document from ToxStrategies that includes further clarifications and follow-up after the ATSAC meeting. We also received an email from the author of the Texas Commission on Environmental Quality (TCEQ) Manganese Development Support Document, Joseph Haney, about the exposure duration adjustment. We wanted to immediately share these documents with you.

Request: Based on these additional materials, we compiled three additional questions for you all to answer. Please read the ToxStrategies response document and TCEQ email to provide full context for the questions.

Please reply-all to this email with your answers to these questions before 4/26.

1. Does Dorman et al. 2005 (see Table 2 specifically) support ToxStrategies' statement on page 3 of their response document?

"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." – ToxStrategies Response pg. 3

If you have questions about Dorman et al. 2005 methods, we attached the paper directly to this email. Figure 1 in Dorman et al. is an overview of the experimental design. Exposure and necropsy procedures are detailed on page 3; for example, Dorman et al. states that "necropsies were performed the day following the last inhalation exposure (i.e., 12-18 hr after termination of the final inhalation exposure)."

2. ToxStrategies highlights TCEQ's guidance related to time adjustments:

"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.'" – ToxStrategies Response pg. 3

Do you agree that the conditions mentioned in this quote from TCEQ guidance are met in the Dorman et al. 2005 and Erikson et al. 2008 study? Do you agree with the TCEQ guidance?

3. Given the additional information from ToxStrategies and TCEQ, what is your current recommendation about an exposure time adjustment and/or uncertainty factors and why?

Attached is a compilation of the three worksheets we received after the 4/3 meeting (see page 2). Please edit the worksheet attachment, if applicable, and email it back to us.

Kearns & West and DEQ are still working on meeting minutes for the 4/3 ATSAC meeting. We will send those to you all to review once they are ready.

Thank you,
ATSAC Governance Team

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May 7, 2024

Mr. Travis Quarles
Bridgewater Group
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SUBJECT: PBPK Modeling Analysis Supports that a Time Adjustment Factor is Not Necessary for the Proposed Manganese Acute TRV

Dear Travis:

As you know, ToxStrategies developed and published an acute guideline for manganese (Mn) of 5 µg/m^3 (Perry et al, 2023)[1], which has been recommended to Oregon Department of Environmental Quality (ODEQ) as a scientific basis for the Agency's 24-hour acute toxicity reference value (TRV). During the Air Toxics Science Advisory Committee's (ATSAC's) April 3, 2024 panel discussion of the Mn Acute (24-hour exposure) TRV, several members questioned whether the point of departure (POD) under consideration should be adjusted for the 6 hour per day duration of exposure in the animal study, and discussed reducing the POD by a factor of four. We previously provided information to you supporting the use of the POD without time adjustment.

This letter presents for consideration the results of our recent additional work to further evaluate the POD using physiologically-based pharmacokinetic (PBPK) modeling. Specifically, we conducted PBPK modeling to replicate the exposure timeframe in the two monkey studies from which the POD was derived (Dorman et al. 2005 and Erikson et al. 2008).[2] We modeled the Mn tissue dose associated with exposure consistent with the monkey studies of 6 hours/day, 5 days/week, for 3 weeks (90-hour scenario) and compared the results to that for a single 24-hour exposure (24-hour scenario) at the proposed acute Mn TRV (5 µg/m^3). Because our previously published modeling results indicated that the highest tissue Mn occurred at approximately 3.375 years of age in males, the 3-10 year age

[1] Perry CS, Blanchette AD, Vivanco SN, Verwiel AH, Proctor DM. 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.

[2] Dorman, DC, Struve MF, Gross EA, Wong BA et al. 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. Respir Res. 6:121. And Erikson, L.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 29:3.

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group was the focus of the additional modeling, and because the POD is for respiratory and neurological effects, we evaluated (and present below) results for the lung as well as all brain regions.

As shown in Figure 1 and Table 1, there is essentially no difference between the model-predicted maximum Mn tissue concentrations for the 90-hour exposure and the 24-hour scenarios in the target tissues of the brain and lung. Mn concentrations in the globus pallidus and lung are predicted to increase slightly above background in both exposure scenarios. But, there is no meaningful difference in Mn concentrations in brain or lung tissues between each scenario or with background (<0.01 µg/g; Table 1). This information provides further support for the conclusion that no time-adjustment to the POD is needed for deriving a health protective 24-hour TRV.

In summary, ToxStrategies' expanded PBPK modeling analysis further supports the conclusion that the proposed TRV of 5 $\mu g/m^3$ is protective for 24-hour exposures to manganese, and that a duration adjustment to the POD is not necessary. In addition, we will be submitting this analysis as a brief communication for publication in *Regulatory Toxicology and Pharmacology*.

Please let us know if you have any questions regarding our additional modeling and results.

Sincerely,

Camarie S. Perry

Camarie S. Perry
Senior Scientist II

Table and Figure

Table 1. Results of PBPK modeling for manganese (µg/g) based on background Mn in ambient air (0.015 µg/m^3), diet, and additional inhalation exposure at the proposed TRV of 5 µg/m^3 for 24- and 90-hour exposures

Modeled Compartment	Male		Female	
	24 hr[1]	90 hr[1,2]	24 hr[1]	90 hr[1,2]
Globus Pallidus	0.535	0.532	0.514	0.511
Olfactory Bulb	0.826	0.823	0.828	0.825
Cerebellum	0.377	0.377	0.379	0.378
Total Brain	0.313	0.313	0.314	0.314
Lung	0.162	0.162	0.156	0.156
Whole Blood	0.0116	0.0114	0.0117	0.0115
Liver	1.20	1.20	1.20	1.20
Nose[3]	4.60	13.3	4.60	13.3
Bone	0.0724	0.0724	0.0734	0.0734

[1] To be consistent, the 24-hour and 90-hour exposures reported in Table 1 were evaluated starting at 3.375 years, which is when the elevated background from the earlier time period for 3-year olds becomes more consistent (Figure 2). The 24-hr exposure values in Table 1 differ slightly from the values in Perry et al. (2023) because the monthly 24-hr exposures in Perry et al. started at three years during which time background exposures were higher.

[2] 6 hours/day, 5 days/week for 3 weeks

[3] The model predicted that that maximum Mn levels in the nose are higher than background, and higher in the 90-hour scenario compared to the 24-hour scenario because tissue half-life in the nose is longer (5 days) than in other tissues. Importantly, increased Mn in nasal tissue did not result in any significant change to levels in lung or brain tissues for either scenario compared to background.

Figure 1: Predicted Mn Tissue Concentrations in 3 to 10 year olds (µg/g)