Oregon Department of Environmental Quality

Air Toxics Science Advisory Committee (ATSAC) Meeting 3 Minutes

April 3, 2024 12:00-2:30 pm PT

The third meeting of the Air Toxics Science Advisory Committee

Meeting Minutes

Meeting Attendees

ATSAC Members	
Jefferson (Jeff) Fowles	New Zealand Food Safety
John Budroe	California Environmental Protection Agency (retired)
John Stanek	Environmental Protection Agency (EPA)
John Vandenberg	Duke University
Qiaoxiang (Daisy) Dong	California Environmental Protection Agency
Susan Tilton	Oregon State University
Project Team	
Ali Mirzakhalili	Oregon Department of Environmental Quality (DEQ)
Apollonia Goeckner	Oregon Department of Environmental Quality (DEQ)
David Farrer	Oregon Health Authority (OHA)
Holly Dixon	Oregon Health Authority (OHA)
J. R. Giska	Oregon Department of Environmental Quality (DEQ)
Kristen Martin	Oregon Department of Environmental Quality (DEQ)
Molly Notarianni	Oregon Health Authority (OHA)
Susan MacMillan	Oregon Department of Environmental Quality (DEQ)
Facilitation Team	
Ben Duncan	Kearns & West
Bianca Valdez	Kearns & West

Meeting slides can be found at https://www.oregon.gov/deq/aq/Documents/ATSACM3slides.pdf

Welcome and Introductions

J. R. Giska, Oregon Department of Environmental Quality (DEQ), opened the third meeting of the Air Toxics Science Advisory Committee (ATSAC) and outlined its purpose: to provide expertise for revising Air Quality Standards, specifically Toxicity Reference Values (TRVs), which regulate industrial emissions of Toxic Air Contaminants. He emphasized that the committee, reinstated in

2021, collaborates with Oregon DEQ and Oregon Health Authority (OHA) in this effort. The meeting focused on a petition concerning the acute, or 24-hour, TRV for manganese. He explained that the petitioners would share scientific materials, followed by a guided discussion among the ATSAC members to inform potential updates to the acute manganese TRV by DEQ and OHA. The ATSAC comprises volunteer toxicology professionals and does not make policy decisions, and the meeting would therefore focus on scientific discussion regarding the petition, excluding policy or fiscal considerations. J.R. thanked the petitioners and ATSAC members for joining and introduced DEQ's AQ Program Administrator, Ali Mirzakhalili.

Ali Mirzakhalili, DEQ, thanked members for attending the meeting to inform DEQ's Cleaner Air Oregon program. He explained the program provides the AQ permitting program with the tools to ensure that DEQ can issue permits that meet health-based standards. Central to this important goal is making sure that DEQ maintains its standards, including the TRVs, based on the most up-to-date science. Ali expressed gratitude for the member's expertise and support and thanked the petitioners for engaging DEQ on this issue.

David Farrer, OHA, welcomed the members and highlighted the strong partnership between OHA and DEQ since the program's inception.

Ben Duncan, Kearns & West (K&W) facilitator, reviewed the Zoom webinar protocols, facilitated introductions from the DEQ and OHA project team, and conducted a roll call of ATSAC members. Ben reviewed the meeting agenda, which included 1) Welcome, 2) Updates on TRV Review, 3) Petitioner Manganese Presentation, 4) Review Tables in Manganese Framing Document, 5) Discussion of Key Questions and 6) Closing and Next Steps.

Updates on TRV Review

Holly Dixon, OHA, provided TRV review updates (slides 4–10). She reminded members of the previous discussion on the TRV review process in earlier ATSAC meetings, seeking feedback on a proposed method for selecting TRVs from multiple sources for acute and chronic exposure. She listed authoritative sources of toxicity information known for their scientific rigor and comprehensive methods, which DEQ considers in setting and updating TRVs. These sources are listed in the Oregon Administrative Rules and were adopted by DEQ's Environmental Quality Commission.
In 2021, the Environmental Quality Commission designated Oregon DEQ, in consultation with ATSAC, as an authoritative source. This grants DEQ and ATSAC greater flexibility in updating TRVs, allowing DEQ, in consultation with ATSAC, to develop TRVs and consider TRVs from entities in addition to the U.S. EPA, U.S. ATSDR (Agency for Toxic Substances and Disease Registry), and CalEPA.

She discussed DEQ's development of the TRV Update Tool, which streamlines the review of existing and newly added TRVs. Over the past year, DEQ has spent considerable time refining this organized Excel spreadsheet, which aggregates and reviews authoritative source information. The tool is designed in a way that allows the user to work on one chemical at a time to reduce the chance of entering data for the wrong chemical. Holly explained how they entered information from each authoritative source for each contaminant with at least one existing or potentially new TRV. She

emphasized how the tool is more than a data entry form, as it allows the user to aggregate information and have a side-by-side comparison to visually confirm changes. DEQ and OHA have completed the data entry and initial TRV decision-making in the tool for all toxic air contaminants that either had existing TRVs in Oregon Administrative Rule or that could potentially have new TRVs. Holly then provided brief updates on their overall progress over the past year. OHA and DEQ carefully considered feedback from the previous ATSAC meeting and subsequently modified both the process and the TRV Update Tool. A summary of changes can be found in the *Proposed TRV Update and Selection Process for ATSAC Review* [1] document. As mentioned previously, the team finished a full initial review of existing and new TRVs. The team reviewed at least four authoritative sources of TRV information by hand for about 1,200 potential TRVs for 400 toxic air contaminants. They reviewed and recorded information on TRV values, critical studies (including information such as date of study, author, and point of departure method used), uncertainty factors, developmental and reproductive hazards, and more. Beginning in early 2024, DEQ and OHA contracted with the Eastern Research Group (ERG) to verify the information recorded by the authoritative sources within the TRV tool. ERG has provided technical support for multiple environmental and health agencies (such as the U.S. EPA and ATSDR) for more than three decades. Holly explained they will share the results of the TRV review with the ATSAC, and all the information shared will have gone through the quality control process. When this quality control process is complete, DEQ and OHA will put together materials for the members to review and conduct a series of ATSAC meetings to discuss the proposals for the TRV updates.

Holly then introduced the petitions for TRV changes. As part of the TRV review process, DEQ Oregon Administrative Rules permit members of the public to submit petitions proposing TRV updates. DEQ welcomed petitions for consideration during the current TRV update process. Petitions were due in late 2022, and DEQ received one petition to change DEQ's TRV for acute exposure (24-hour) to manganese (hereafter 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 were provided by ToxStrategies, a scientific consulting firm. The petition proposes to increase the DEQ acute manganese TRV from 0.3 µg/m^3 (micrograms per cubic meter) to 5 µg/m^3. The 5 µg/m^3 is consistent with the 24-hour ambient monitoring comparison value developed by the Texas Commission of Environmental Quality (TCEQ). 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 in the framing document.[2] Staff at ToxStrategies also published a peer-reviewed manuscript in 2023 on this acute TRV development ("Perry et al."). The manganese acute TRV proposed by Perry et al. is also equivalent to the TCEQ TRV and petition TRV. However, Perry et al. propose a slightly different set of UFs than the ones used by TCEQ and by the petitioner, which are discussed in detail in the framing document. Holly concluded by explaining members would now receive a presentation on the petition from ToxStrategies, with DEQ and OHA looking forward to ATSAC's feedback on the matter.

Petitioner Manganese Presentation

Ben, K&W facilitator, introduced ToxStrategies presenters Ann Verwiel and Camarie Perry, and Travis Quarles from Bridgewater Group. Ben explained in the fall of 2022, as part of the TRV Review and Rulemaking, DEQ solicited petitions from the public to add or remove chemicals from the Priority

List of chemicals, to remove a chemical from the TRV list, or to revise or add a TRV. The Bridgewater Group submitted a petition to change the acute value of manganese, and the information included in that petition was prepared by Tox Strategies, who will be talking to ATSAC about their methodology. Ben explained the petitioners would have a half hour to present and members to participate in a question-and-answer session. Ben encouraged ATSAC to ask questions about the Petitioner's proposals for UFs.

Travis Quarles, Bridgewater Group, opened the presentation by thanking staff and ATSAC members for their time and for the opportunity to present the petition.

Camarie Perry, ToxStrategies, presented on the *Derivation of Manganese 24-hour Acute Inhalation Guideline*[3] (slides 12-31). As opposed to most other regulated compounds, Camarie noted that manganese is unique, as it's an essential nutrient and is necessary for the proper functioning of the body. It has a U-shaped dose-response curve, therefore, too little or too much of this nutrient is problematic and levels in the body need to be kept in the middle of the range. ToxStrategies stated that an air level of 5 µg/m^3 would not increase a person's internal stores of manganese. This proposed level would be health-protective for years of exposure. DEQ's preference is that acute guidelines be developed from acute toxicity studies; therefore, ToxStrategies', short-term value is based on short-term studies.

Camarie further introduced herself and her background, highlighting her experience as a state regulator for the Texas Commission of Environmental Quality (TCEQ) and a consultant. She also introduced her colleague Ann Holbrow Veriweil who has over 20 years of experience in environmental risk assessment consulting. Both Camarie and Ann have extensive experience in human health risk assessment, evaluation of air emissions, developing remediation guidance, exposure and toxicity evaluations, and metals.

Camerie presented on general manganese toxicity, reiterating that it is an essential element that is beneficial at low concentrations and its absorption and excretion are controlled by homeostasis. Manganese is critical for neurodevelopment and exhibits an inverted U-shaped dose-response curve. During development, both manganese deficiency and excess can result in neurocognitive effects. Through homeostasis, systemic background levels are in the optimal range for health. Since manganese toxicokinetics are non-linear, derivation of toxicity criteria has been challenging as standardized UFs are not always applicable. Neurological effects are the most sensitive endpoints for chronic exposures, but respiratory effects can occur with acute exposures.

She shared that ToxStrategies' objective was to develop a 24-hour acute health guideline value protective of respiratory and neurological effects and use current physiologically based pharmacokinetic (PBPK) models to address potential manganese accumulation in critical brain compartments such as the globus pallidus during sensitive developmental life stages. They derived an acute, 24-hour guideline for manganese inhalation exposure of 5 µg/m^3 based on 3-week (90-hour) monkey studies evaluating respiratory effects (Dorman et al. 2005) as well as oxidative stress markers in the brain (Erikson et al. 2008). She noted the group would discuss UFs in more detail later. The PBPK modeling was used to confirm that 5 µg/m^3 acute exposures do not significantly increase manganese in brain tissues (e.g., globus pallidus – primary target tissue for manganese accumulation & neurotoxicity).

She provided further information on the PBPK modeling. PBPK models predict manganese accumulation in sensitive brain compartments, including the globus pallidus, from oral and inhalation exposures, and for multiple life stages. PBPK models are particularly useful for manganese to address the challenges of assessing manganese accumulation considering homeostasis and potential neurotoxicity (Yoon et al. 2019; Campbell et al. 2023). From Yoon et al. (2011 and 2019), ToxStrategies used the "lactation/infant" and the "child/adolescent/adult" model codes, respectively. ToxStrategies focused on the child/adolescent/adult model code because it predicted higher globus pallidus concentrations. They evaluated potential outcomes for two short-term exposure scenarios at 5 µg/m^3 manganese.

1. Monthly exposure scenario: A 24-hour inhalation exposure one time per month, from birth throughout life, with diet and ambient air exposures set to background levels.
2. 3-Week exposure scenario: A single, 3-week period of constant inhalation exposure at age 3, since the model predicts the highest manganese levels in globus pallidus at ~3 years of age, with diet and ambient air exposures set to background levels. (*Scenario with highest tissue manganese accumulation.)*

Camarie presented the PBPK modeling results (slide 17) with a figure from the Perry et al. 2023 publication. The figure displayed the highest concentration from the 3-week exposure scenario from males aged 3-5 with the highest manganese concentrations in the globus pallidus. The highest background concentration was 0.535 µg/g, and the highest modeled concentration was 0.552 µg/g, which was 3 percent above background in the globus pallidus. Therefore, neither exposure duration (24-hour exposure monthly or 3-week continuous exposure) results in manganese concentrations significantly above background exposures. The predicted manganese levels in the globus pallidus are lower than the tissue-based no-observed-adverse-effect levels (NOAELs) for neurotoxic effects in humans and monkeys which range from 0.7-0.9 µg/g (Gentry et al. 2017, Schroeter et al. 2012). Therefore, an acute TRV of 5 µg/m^3 even with 3 weeks of continuous exposure would not result in significant exposures above background or NOAELs in humans and monkeys. She also presented a bar graph of the predicted manganese tissue concentration in 3 to 10-year-olds (µg/g). Multiple brain tissues and whole blood and liver tissue concentrations of manganese were not above background under either exposure scenario.

Next, she referenced DEQ's framing document, which summarizes information relevant to the proposed manganese acute TRV. She highlighted the following from the document:
"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 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."

Camarie then discussed the uncertainty factors, or UFs, used. Individual UFs are not completely independent of each other. This is especially true for essential nutrients which display a U-shaped dose-response curve and combining default UFs of 10 can lead to double-counting. Therefore, EPA, OEHHA, and TCEQ have developed upper limits on total UFs for inhalation guidelines. For example, both EPA (2002) and OEHHA (2008) limit total UFs for chronic inhalation exposures to 3,000.

Similarly, TCEQ limits total UFs for acute inhalation guidelines to 300. As ToxStrategies' understanding of the issues has expanded over time, they're recommending the same guideline of 5 µg/m^3, but slightly different UFs between the petition and the publication (Perry et al. 2023).
There are various UFs for determining proposed acute guidelines for manganese. Camarie presented the UF options across the various entities. The chart presented values from ODEQ's proposed range of potential options, TCEQ's (2017) 24-hour guideline, ToxStrategies' support for Petition to ODEQ (Nov. 1, 2022), and the proposed 24-hour Acute Guideline for manganese (Perry et al. 2023). She noted they assumed a mild lowest-observed-adverse effect level (LOAEL) of 1.5 mg/m^3 and then reviewed UF options. The colored columns in the chart (slide 21) indicate three individual UFs (i.e., UF_A, UF_L, and UF_D) that differ between the various entities.

Camarie then reviewed the three different UFs, reviewing the recommended value and rationale for each. Below is a table with this information:

Uncertainty Factor	Recommended Value	Rationale
Interspecies (UF_A) Range in Framework Document: 3 - 10	3	A UF_A of 3 was used since monkeys largely replicate the toxicodynamic neurobehavioral effects of Mn observed in humans (Schroeter et al. 2011; Gentry et al. 2017) (UF_{A-D} of 3), and toxicokinetics between monkeys and humans in the Dorman et al. (2005) and Erikson et al. (2008) studies are essentially equivalent (UF_{A-K} of 1). PBPK modeling was used as an additional line of evidence supporting consistent toxicokinetics between monkeys and humans.
LOAEL to NOAEL (UF_L) Range in Framework Document: 2 - 10	10	Although effects were mild, a UF_L of 10 was used for conservatism and protectiveness, and since PBPK modeling showed tissue Mn levels did not immediately return to background levels following cessation of the 3-week continuous exposure (returned to background in <6 months). This is a conservative assumption, since the respiratory effects were mild, and no clinical effects were observed in monkeys in the Dorman et al. (2005) and Erikson et al. (2008) studies and the lack of data for a continuous 24-h exposure period. Due to the study designs of Dorman et al. (2005) and Erikson et al. (2008), post-

		exposure recovery data are not presented for the 90-hour exposure group.
Database (U_D) Range in Framework Document: 1 - 6	1	General Considerations: Database insufficiency factor – “Adjusts for the possibility of identifying a lower (or more sensitive effect) if additional studies were available” (Dankovic et al. 2015). In determining UF_D - Evaluate the specific kinds of available data and weigh the likelihood that additional studies would reveal more sensitive toxicity/endpoints. A UF_D of 1 was used because it is considered unnecessary to impose a UF_D factor for reproductive or developmental effects. 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. Similarly, Chung et al. (2015) observed neurocognitive deficits among the offspring of mothers with low and high blood manganese relevant to the U-shaped dose-response curve. Although this uncertainty is not specifically accounted for, an additional uncertainty factor is not likely necessary because the PBPK modeling demonstrates that tissue Mn levels (blood, liver and brain including the globus pallidus) are not affected

		significantly at 24-hour exposures of 5 µg/m^3.

Camarie explained their proposed acute guideline of 5 µg/m^3 is low compared to published chronic inhalation values from the following literature:

- Bailey et al. (2009) proposed 2 µg/m^3 to 7 µg/m^3 as chronic reference concentrations.
- Schroeter et al. (2011) and Gentry et al. (2017) predicted that homeostasis maintains manganese levels in the brain target tissue at airborne concentrations below 10 µg/m^3.
- Yoon et al. (2011) indicates that maternal and fetal blood manganese levels are not affected at airborne concentrations less than 10 µg/m^3.

In summary, Camarie concluded that by using PBPK methods, this study supports a 24-hour acute guideline for environmental exposures of 5 µg/m^3, which is equal to the value set by the TCEQ. Essential nutrients have unique pharmacological and toxicological properties and therefore require alternative considerations in setting guideline levels and consideration of background tissue concentrations that are beneficial. The PBPK modeling demonstrates that the guideline is protective of both respiratory and neurological effects, as manganese is not expected to accumulate in key tissues. ToxStrategies recommended a combined UF of 300 applied to the point of departure (POD) of 1.5 mg/m^3, based on the following individual UFs:

- UF_A: 3 for similarities in neurobehavioral effects and toxicokinetics between monkeys in humans
- UF_H: 10 for sensitive human subpopulations (conservative due to PBPK modeling for sensitive life stages.)
- UF_L: 10 for mild LOAEL to NOAEL (conservative)
- UF_S: 1 since key study was 90 hours (longer than target of 24 hours)
- UF_D: 1 since manganese is an essential nutrient and necessary for development. PBPK modeling indicates that the proposed 24-hour guideline of 5 µg/m^3 is not expected to significantly increase critical brain compartment, blood and other tissue compartments over background or NOAELs; and the guideline is low compared to chronic thresholds.

Ben thanked ToxStrategies for presenting and opened the meeting for discussion. He reminded the members that the petitioners would be available for the remainder of the meeting.

Below is the question-and-answer session that followed:

- **John Vandenberg** inquired about ToxStrategies reasoning for selecting an exposure occurring once per month throughout life (monthly exposure scenario) throughout life for the PBPK model.
    - **Camarie Perry** explained that a monthly exposure scenario was what they felt would be appropriate to align with the 24-hour regulatory guideline concentration, representing a reasonable level of exposure. Additionally, the existing acute TRV was derived from data spanning five years of exposure. ToxStrategies also incorporated a three-week continuous exposure scenario to address the timeframe considered by ODEQ, ensuring a conservative approach.
    - **Ann Holbrow Veriweil** agreed and noted that, from a regulatory standpoint, if a facility occasionally exceeds acute guidelines once a month, it raises questions about the operational status. Similarly, being consistently at the acute guideline level for an extended period, such as a few weeks, prompts considerations of compliance with the chronic TRV. Acute guidelines are intended for short-term, unusual situations.

- **John V.** asked if the six-month period until levels returned to background occurred after the three-week or 24-hour exposure.
    - **Ann V.** clarified it was after three weeks, and the focus of today's presentation was on the worst-case scenario in the PBPK modeling.
- **John V.** noted discontinuity around 3.25-3.5 years of age, where model concentrations abruptly increased. He inquired on the cause of this occurrence.
    - **Ann V.** explained the person most familiar with the model is not available, however, she would reach out to them with this question.
    - **Jeff Fowles** noted it might have to do with infancy or early childhood breastmilk exposure.
    - **Ann V.** responded that the graph depicts a three-week exposure for a 3-year-old child, so that is not considered a potential exposure at that point in time.
- **Jeff F.** asked about the selection of background or dietary levels of manganese in the primate's diets. He inquired if the background levels in the modeling explored the upper limits of what would be considered normal in a typical human diet.
    - **Ann V.** explained the background levels in the modeling are based on levels used by PBPK modelers who wrote the papers. Regarding the comparison to background levels in the studies from which the point of departure was derived, ToxStrategies did not make that comparison directly but relied on modelers to provide them with typical ambient background exposures.
    - **Jeff F.** acknowledged that the conclusions would remain the same even if the background is higher.
- **John Budroe** added a clarification to a ToxStrategies slide that referenced other agencies having cumulative uncertainty factors and the issue of double counting. John B. stated that he knows that OEHHA (and thinks that IRIS is similar) does not have a cap on cumulative uncertainty factors. Instead, if a cumulative uncertainty factor becomes larger than 3,000, then the data set is considered to be too uncertain to derive a TRV, either chronic or acute. Overall, it's not an uncertainty factor interactivity concern and it's not an uncertainty factor cap, it's more that OEHHA uses the total uncertainty factor to decide whether or not to use the dataset.
- **Daisy Dong** noted that two studies in the petition (Erikson et al. 2005 and 2006) involve in utero exposure. She asked if ToxStrategies looked further into those studies and others (including rat studies) for more information on in utero exposures and endpoints. For manganese, the neurological effect is clearly related to oxidative stress, so did ToxStrategies look into any of those gene expression reports?
    - **Camarie P.** explained that rat studies may not be as applicable to humans as studies involving monkeys. There's less emphasis on rat studies to replicate human neurotoxic effects, especially concerning breathing given toxicokinetic differences. Each species reacts differently, so if they pursued rat studies, they would focus on in utero exposure and potential developmental effects.
    - **Daisy D.** responded that the monkey study only provides a single dose, which is a limitation of the critical studies, and noted it would be good to see some endpoint related to *in utero* exposure perhaps in rodents.
- **Daisy D.** asked why there was no exposure time adjustment to account for monkeys in the study being exposed for 6 hours a day while the toxicity value being derived is for an exposure period of 24 hours. She stated that it is standard practice for EPA and CalEPA to adjust for exposure time duration, whether in animal or human studies.
    - **Ann V.** explained that the animals underwent continuous exposure over several days, although there may have been periods within each day where they were not exposed. The exposure was repeated day after day, and it's noted that manganese levels do not return to the background immediately. This kind of intermittent exposure was sufficiently relevant.

- **Daisy D.** noted that unless there's a strong reason not to, it's crucial to adjust the duration from 6 to 24 hours. Tissues may fully recover within shorter periods, and longer exposures can have different effects. Regulatory agencies, like the EPA, routinely adjust for duration in their assessments. This adjustment is essential for accurately interpreting exposure data.
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Review Tables in Manganese Framing Document

Holly Dixon, OHA, provided a brief refresher on all the different tables in the framing document (slides 32-36). The first table compiles key information on the critical studies used in the TRVs for acute exposure to manganese. Both TCEQ and the petition use the same critical study (Dorman et al. 2005) and Perry et al. use two critical studies (Dorman et al., 2005; Erikson et al., 2008).
While TCEQ, the petition, and Perry et al. all use the same point of departure, they all use different uncertainty factors to calculate a 24-hour acute manganese TRV. The differences and similarities in UFs are summarized in Table 2.

Holly then presented Table 3, noting a large portion of it comprises quotes from TCEQ on why they included a database UF. Table 4 includes potential options for DEQ's acute manganese TRV. Holly noted that several of the ATSAC discussion questions relate to the options in this table. She highlighted the last row as an area for members to consider other options that they would prefer over the existing listed options. She concluded by highlighting the last three pages of the framing document go into more detail on considerations for specific UFs.

Discussion of Key Questions

Ben facilitated the ATSAC members' responses to the prepared discussion questions. He also reminded the members of the discussion worksheet where they can fill out their answers and share them with DEQ. Members were asked the following questions:

1. What critical study option in Table 1 do you like the best and why? Would you propose another option for DEQ to consider?
2. Do you think the UF_A (interspecies) should be 3 or 10 or something else? Why?
3. Do you think the UF_H (intraspecies) should be 10 or something else? All proposals in Table 4 have a UFH of 10.
4. Do you think the UF_L (LOAEL) should be 2, 3, 10, or something else? Why?
5. Do you agree with the petitioners that there is enough evidence to not have a UF_D? Why or why not? Do you agree with the TCEQ UF_D of 6? Why or why not?
6. Do you think we should put a cap on the maximum total UF like TCEQ does?
7. 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?

Below are the ATSAC member's responses to the discussion questions.

John Budroe, **CAL EPA (retired)**

1. John noted that neither ATSDR nor OEHHA decided to pursue acute toxicity value derivation. ATSDR stated that the available data on the toxicity of inhaled manganese was considered insufficient for deriving an acute intermediate duration inhalation MRLs. Dorman 2005 and Erikson 2008 are not especially good studies; these studies have a freestanding LOAEL with no controls. If

DEQ needs to derive an acute TRV that is not from a chronic TRV, then Option 4 with cumulative UFs at 1800 is recommended and would result in a TRV of 0.8 µg/m³.
2. John recommends using a UF_A of a square root of 10. He followed OEHHA REL methodology; a square root of 10 is used for this UF when the data is from non-human primates.
3. John broke his response into two parts: toxicokinetics and toxicodynamics. For toxicokinetics, he suggested applying the square root of 10 to account for residual susceptibility differences and we have some degree of information from PBPK modeling, but it wasn't directly used to develop an internal dose that the TRV is based on. For toxicodynamics, it should also be 10 to account for potential additional susceptibility differences, especially in children; in this situation, both the respiratory system and nervous system can be impacted by early life exposure in children. This should result in a combined UF_H of 30.
4. John recommended a UF_L of 6 because OEHHA would consider this a mild effect LOAEL.
5. For the UF_D, John noted that the framing document highlights that there is substantial uncertainty regarding the potential for neurodevelopmental toxicity in humans. He referenced a study (Takser et al. 2003[4]) that found a correlation between higher manganese levels in cord blood and reduced psychomotor development at three years of age, and there are several other human studies that show the potential for neurodevelopmental effects from manganese exposure. This indicates that there is a current lack of animal or quantitative neurodevelopmental data. John recommended a UF_D of 3 in all the proposed TRVs as a minimum.
6. As mentioned earlier, OEHHA does not cap cumulative UFs, but does not develop toxicity values for chemicals when the cumulative UF goes over 3,000. John thinks that the IRIS program at the U.S. EPA follows a similar approach. John thinks that a similar approach as OEHHA is greatly preferable instead of capping the cumulative UF at 300 or some other value.
7. Regarding the proposal option, John recommends a cumulative uncertainty factor of 1800, therefore a TRV of 0.8 µg/m³ is recommended.
8.

Holly D. mentioned that DEQ and OHA want to know if ATSAC members have concerns with the critical studies in Table 1 and if anyone would prefer if DEQ continues to adapt a chronic TRV for the acute TRV or not have an acute TRV altogether.

Dave F. responded to John B.'s comment that these studies are not great, and there are reasons they weren't used to create an acute value. He noted if they didn't use the studies, their option would be to not have a number for acute manganese or stick with a modification of the existing chronic value, and that modification does have a lot of uncertainty.

Daisy Dong, CAL EPA

1. Daisy agreed with combining both studies (Dorman et al. 2005 and Erikson et al. 2008). Daisey 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. Daisy agreed with the 1.5 mg/m³ point of departure (POD) value; however, she disagreed with the petitioner's proposal not to adjust for the exposure time duration. Daisy supported incorporating an exposure time adjustment to adjust from6 hours of exposure to a 24-hour TRV.
2. The interspecies UF_A should be 3 because primates are very similar to humans, and essentially already doing the human equivalent concentration calculation. A UFA 3 accommodates the possible toxicodynamic differences between monkeys and humans.

3. Daisy supported an intraspecies UF_H of 10, which she states is very conventional.
4. She recommended the UF_L should be 10 as the earlier presentation summarized and given that it is a one dose study.
5. Regarding the UF_D, Daisy gave weight to the PBPK modeling. Daisy has expertise in PBPK modeling. Every model has uncertainty. However, compared to other chemicals, these manganese PBPK models are actually quite good and included many different variables such as diet contribution and different manganese forms. Daisy liked the approach of modeling 5 ug/m^3 exposure for the different scenarios. At this exposure level, not much change in manganese concentration was observed in the brain. She does not think additional studies are needed for the UF_D.
6. As John mentioned, Cal EPA does not have a cap on cumulative UFs. In California, when the total UF exceeds 3000, we don't use that critical study because there is too much uncertainty. Daisy suggests avoiding a cap on the UF, because it may lead to an unacceptable level of uncertainty and the data cannot be used.
7. Daisy proposes a new option to include an exposure duration adjustment, which is standard practice. She chooses the same UFs that were selected by the ToxStrategies' group (Perry et al. 2023). Her acute TRV proposal is 1.25 ug/m^3.

John Stanek, EPA

1. John noted that Dorman et al. 2005 and Erikson et al. 2008 are the available studies, but they have limitations. It is difficult to call the POD a LOAEL in this case because you have a control and one dose, which is because only one dose was considered during a 15-day exposure period. John expressed uncertainty about whether this information could support setting the LOAEL at 1.5 ug/m^3. There might be some indication of a NOAEL by looking closely at the two studies. Overall, the database is limited. Modeling could be helpful, but it's crucial to understand how reporting levels in the brain regions might protect against respiratory effects.
2. Not answered at this point in meeting.
3. Not answered at this point in meeting.
4. Not answered at this point in meeting.
5. Not answered at this point in meeting.
6. To reiterate John Budroe's and Daisy's point, when the cumulative UF exceeds 3000, then the EPA will not derive a toxicity value because there is too much uncertainty. Based on John's experience, other agencies do sometimes rely on a single published guideline for acute exposure guideline levels (e.g., OECD, AEGLs). They typically focus on a couple of uncertainty factors like interspecies and intraspecies differences.
7. In agreement with Daisy, a significant concern is the lack of an adjustment to a 24-hour duration. At a minimum 6 to 24-hour duration adjustments should be made, although John is unsure if a 5 out of 7-day adjustment is necessary, considering the study's three-week duration. John noted that he spoke with EPA colleagues about the lack of the 6 to 24-hour exposure duration adjustment and they could not figure out why it was not included; EPA would incorporate the adjustment for any scenario. With uncertainty factors in play, the acute TRV could be either 1.25 or 0.9 ug/m^3.

Jeff Fowles, New Zealand Food Safety

1. Jeff acknowledges that relying on a single-dose study is not ideal but after considering that these critical studies include primate data and a fairly well-developed PBPK model, he believes it can work.
2. Jeff stated that the UFs in Option 6 of Table 4 seem reasonable, which is the Perry et al. 2023 option. By supporting Option 6, Jeff recommends a UF_A value of 3.
3. By supporting Option 6, Jeff recommends a UF_H value of 10.

4. Jeff is thinking about the points John S. made about the LOAEL and NOAEL and wonder if more work could be done to explore further reducing the UF_L.
5. He noted the UF_D is not justified in this case.
6. Jeff does not support a cap because it is inevitably arbitrary. Even though, as mentioned in the ToxStrategies presentation, UFs may overlap with one another, it is very difficult to tease that apart. UFs may overlap as it's difficult to distinguish between factors and to impose a cap would be arbitrary.
7. Jeff supported Daisy's comment that there needs to be a time adjustment from 6 to 24 hours. If there is no time adjustment, there needs to be good justification as to why not. He recommended a modified Option 6 if there is a time adjustment added.

Question and Answer

- **John V.** noted the frequency of questions regarding the duration adjustments and suggested asking the petitioners for their reasoning.
- **Holly D.** said that she cannot comment on what the petitioners did, but explained she has found excerpts from TCEQ documents on why a duration adjustment was not included in the TCEQ acute TRV that may help the group. She shared the following quotes:
    - This excerpt is from the TCEQ Manganese Development Support Document[5].
        - "This minimal LOAEL will be applied to exposure durations up to 24 hours of exposure since study data demonstrated that the accumulation of manganese in the lung predominated over the 90-h total, 3-week exposure period."
        - "That is, after 15 exposure days, lung manganese was statistically significantly increased over controls, demonstrating that the toxicokinetic clearance did not occur after each daily 6-h exposure but rather that manganese accumulation in the lung occurred from day to day, and in fact appears to have reached steady state (see table 2 of Doman et al 2005), supporting the use of results from this 90-h total exposure for the derivation of a 24-h value."
    - This excerpt is from the TCEQ Guidelines to Develop Toxicity Factors[6].
        - "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 can be used as the 24-h POD. No duration adjustments will be made."
- **Holly D.** asked ATSAC members for their opinions on this. She noted the petitioners likely did not adjust the time if it was reasonable to assume a steady state had been achieved.
    - **Daisy D.** does not think the TCEQ argument is very strong because we do not have the data in this case to know if a 24-hour manganese exposure is completely different from a 6 hour manganese exposure.

John Vandenberg, Duke University

1. John expressed concern about the modeling's lack of consideration for prenatal and infant exposures up to the age of 3. He mentioned that a sensitive population might be overlooked and referred to the National Institute of Health guidelines on manganese, which outline exposure levels in the diet considered necessary for normal intake but also highlight upper tolerance intake levels for ingestion. He pointed out the significant decrease in upper intake levels for younger children and questioned if the modeling accounts for this. He wondered if this aspect is applied as a UF_D or UF_H. However, he's unsure where this fits in exactly, and he's concerned about the lack of data available for infants.
2. John supports a UF_A of 3.

3. He supports a UF_H of at least 10, raising concerns about exposure to prenatal and infants. He notes that the UF_H could potentially be higher than 10 and is in support of John Budroe's comments on this UF.
4. Not answered at this point in meeting (see page 16).
5. John is concerned about the lack of data for infants, which could be included as part of the UF_D.
6. Not answered at this point in meeting.
7. He thinks there should be more discussion on the need for a duration adjustment. He concluded by stating that he doesn't have a definitive conclusion at this point, as different possible options yield UFs ranging from 900 to 1000 or possibly higher.

Susan Tilton, Oregon State University

1. Susan was comfortable considering the two studies that were included in the Perry et al. paper that were used to derive the LOAEL for respiratory effects.
2. Regarding the interspecies uncertainty factor UF_A, Susan agrees with an uncertainty factor of 3. She notes that dosimetry adjustments are not needed in this case and supports a threefold factor for toxicodynamics.
3. She shared support for the intraspecies UF_H of 10; however, noted some of the data is under consideration in the last UF.
4. Concerning the UF_L, Susan understood that part of the rationale for employing a tenfold factor was due to the absence of a 24-hour exposure scenario in the relied-upon studies. She believed there was consideration for this uncertainty incorporated into the decision. Given the single-dose basis, the observed effects leading were identified as mild or reversible.
5. Regarding the UF_D, Susan reflected on the need for adjustments to assist the potential identification of more sensitive effects if additional studies were accessible. She noted that the PBPK modeling utilized here is quite strong, which incorporates various models, exposure routes, tissue concentrations, and brain regions. However, Susan acknowledged limitations. Susan agreed with other ATSAC members that the modeling is not addressing the full potential for in utero exposure and endpoints. There is uncertainty regarding the most sensitive route of in utero exposure.
6. Not answered at this point in meeting.
7. Susan has not come to a conclusion yet. She said that many of her comments align with Option 6 but has some reservations.

Questions and Answers:

Ben facilitated further discussion and reflection between ATSAC members.

- **John S.** noted uncertainty on the rationale of the duration adjustment that was in the TCEQ documents. He explained that any exposures via particle inhalation will have some clearance upon cessation of exposure. Steady-state levels reflect exposure with clearance. Even for chronic studies we assume pseudo-steady-state conditions. John stated he does not find the TCEQ argument for no duration adjustment compelling enough. He thinks the bar needs to be high to not do a duration adjustment and he does not see the evidence for that here given such a limited database. It would be highly unusual not to adjust the duration based on guidance from other agencies.
- **Daisy D.** added that for EPA and other agencies' acute guidelines, weekly adjustments from 5 to 7 days are not done, only hourly duration adjustments.
- **Jeff F.** asked what the group thinks about looking at this chemical as a traditional risk assessment exercise with the application of UFs. Considering manganese is an essential nutrient and systemic exposure would be from the diet, is it beneficial to evaluate the TRV values and determine the level of daily exposure? Given that humans intake this nutrient daily, normal dietary levels range from 1 mg/day to 3 mg/day, with adverse effects expected around 8 mg/day. If the

proposed TRV is 5 µg/m³, and the inhalation rate is 20 cubic meters per day, this translates to about 100 micrograms, which is approximately 10% of the nutritional adequacy daily.
    - **Dave F.** highlighted that the route of exposure with manganese is different. All oral exposure goes through the liver, which regulates manganese levels in the body. Humans are intended to ingest manganese and not inhale it to reach nutritional levels.
    - **Daisy D.** reiterated that exposure route is an important consideration here and added that ingesting manganese (rather than inhaling it) makes it less likely to end up in the brain. She noted that the PBPK model incorporated the background already from the diet and the air. The background is about 0.5 µg/m³. Inhalation of manganese has different effects on the body, particularly the nervous system.
- **Ben, K&W facilitator,** reflected on the discussion and asked members if they had any other comments on the time duration adjustment questions and concerns that had been raised in the meeting.
- **John V.** noted that the duration adjustment is not a UF, it's changing the TRV starting point, the POD. The POD would then be 0.375 ug/m^3 instead of 1.5 ug/m^3.
    - **Daisy** confirmed that the POD would be reduced to 0.375 ug/m^3 from 1.5 ug/m^3 after applying a duration adjustment from a 6-h to a 24-h exposure duration.
- **John V.** reported out where he is landing for UFs as the meeting wraps up: UFA of 3 because of the monkey data, UFH of at least 10 because he is concerned about exposure to infants and prenatal, and UFL of 10 because it's a freestanding LOAEL. Currently, he is thinking about a total UF of 300 applied following the duration adjustment POD.
- **John S.** agreed that John's UF selections are similar to where he is landing as well. He advised the group that we have to be cautious about what to lump into an UF. John stated that at EPA they try to avoid just trying to bend something into another UF because they are not sure where it fits.
- **John V.** noted that some of these measures are from these studies, and he highlighted the gap in neuro-behavioral study effects.
    - **Holly D.** asked if the lack of neurobehavioral studies fits in the UFD category.
    - **John V.** explained there will always be gaps, and working with primates is good despite them being juveniles. He recommended a UF_A of 3 and to add at least 3 for the UF_D. He added that he appreciated John S. comment on not co-mingling the different UF categories, but they do relate to each other.
- **John B.** emphasized the lack of neurodevelopmental data and if this does not go into UF_H, then it should be considered in UF_D.
- **Holly D.** inquired about the size considerations for those who support UF_D.
    - **John V.** answered to use 1, 3, or 10.
    - **Susan T.** requested to consider the available reproductive and developmental data that exists that suggests it's not a concern. The focus should be on areas where uncertainty exists and we don't have data, particularly concerning potentially sensitive exposure windows.
    - **Daisy D.** answered 1.
- **John V**. inquired about the nature of the manganese sources in Oregon.
    - **J.R.** responded that the majority of manganese emissions come from biomass boilers, and other sources include foundry operations and shredding metals.

Ben, K&W facilitator, thanked everyone for their answers and feedback. He noted that members should feel free to fill out the worksheet and email it to Apple Goeckner at DEQ, noting the instructions are on the worksheet. He reminded the members that the worksheet is optional, but helpful if members fill it out. He asked if there were any final thoughts before moving on to next steps and closing.

Closing and Next Steps

Apple, DEQ, thanked the ATSAC members for their thoughtful discussion and feedback. DEQ will consider everything they heard. This month DEQ will be writing and editing the meeting minutes from today's meeting and will circulate a draft to members to ensure the minutes are accurate.
DEQ will work on a proposal for the acute manganese TRV that will be presented to a rules advisory committee and later to DEQ's governing board, the Environmental Quality Commission. DEQ will keep the members updated on what their proposal will be, likely via email.

Apple also shared information about the next series of ATSAC meetings they will plan once the quality control processes wrap up. DEQ anticipates having a series of at least three meetings in the fall of this year where they will discuss the findings from the TRV review and selection process. Apple noted they envision that at the first meeting, DEQ will orient members to the files/tables prepared for their review. She noted for this meeting, members would not need to do any prep work. DEQ will show the materials they have prepared and answer any clarifying questions. DEQ will plan on the second meeting in the series being a few weeks after the first one so there is plenty of time to review the materials. At this meeting, DEQ hopes to get feedback from members on the overall process that DEQ followed to update TRVs including QC. DEQ also hopes to document ATSAC feedback on the proposed TRVs for individual TACs. The third meeting in the series will reserve more time to discuss other challenging contaminants, like PFAS, diesel particulate matter, etc. Apple will update ATSAC members via email to schedule these meetings. She concluded by thanking members for the great discussion today.

Ben thanked everyone for participating and adjourned the meeting.

[1] Proposed TRV Update and Selection Process for ATSAC Review
https://www.oregon.gov/deq/aq/Documents/ProposedTRVforATSAC.pdf
[2] Framing Document for DEQ's Air Toxics Science Advisory Committee
https://www.oregon.gov/deq/aq/Documents/ATSAC-ManganesePetition.pdf
[3] Derivation of manganese 24-hour acute inhalation guideline protective of respiratory and neurological effects. https://www.sciencedirect.com/science/article/pii/S0273230023001861
[4] Manganese, monoamine metabolite levels at birth, and child psychomotor development.
https://www.sciencedirect.com/science/article/abs/pii/S0161813X03000585
[5] TCEQ Manganese Development Support Document, 2017.
https://www.tceq.texas.gov/downloads/toxicology/dsd/final/mn.pdf
[6] TCEQ Guidelines to Develop Toxicity Factors,
2015. https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf