Summary of Meeting Action Items

Event Title: Manganese (Mn) Physiologically based pharmacokinetic (PBPK) Modeling Updates
Date: November 16, 2018
Time: 9:00 PM – 12:00 PM
Keywords: IRIS, Manganese
Participants:

Harvey Clewell- Ramboll
Robinan Gentry- Ramboll
Cynthia Van Landingham- Ramboll
Mel Andersen- Andersen ToxConsulting
Miyoung Yoon- ToxStrategies
Athena Keene- Afton Chemical Corporation
Michael Taylor- NiPERA
Annie Jarabek – US EPA, ORD NCEA
Tina Bahadori- US EPA, ORD NCEA
Kris Thayer- US EPA, ORD NCEA
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John Vandenburg- US EPA, ORD NCEA
Viktor Morozov- US EPA, ORD NCEA
Santhini Ramasamy- US EPA, ORD NCEA
Paul White- US EPA, ORD NCEA
Paul Schlosser- US EPA, ORD NCEA
Tom Bateson- US EPA, ORD NCEA
Yu-Sheng Lin- US EPA, ORD NCEA
James Brown- US EPA, ORD NCEA
William Boyes- US EPA, ORD NHEERL
Marion Hoyer- US EPA, OAR
Darcy Smite – US EPA, OAR

Summary of meeting activities and next steps:

- EPA Presentations
  - Quality Assurance Project Plan (QAPP) for PBPK Models, Paul Schlosser, U.S. EPA (slides attached and QAPP is available at https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4326432)
  - Development of Manganese Pharmacokinetic Data under Section 211(b) of the Clean Air Act (CAA), William Boyes, U.S. EPA (slides attached)
- Ramboll/ToxStrategies/Mel Anderson slides (attached as one set of slides)
  - Background on Mn PBPK Models and Applications to Evaluate Safe Exposures, Harvey Clewell, Ramboll and Miyoung Yoon, ToxStrategies
  - Sensitivity Analysis for the Published Adult Human Mn Model, Cynthia Van Landingham, Ramboll
  - PBPK Modeling of Bioavailability of Mn in Diet and Drinking Water, Miyoung Yoon, ToxStrategies
  - PBPK Modeling for Mn with Rapid Association – Dissociation in Tissues, Mel Andersen, Andersen ToxConsulting
- Items for Discussion and Next Steps
  1. EPA indicated there are no imminent plans for release of an IRIS Assessment Plan for Mn. The Assessment Plan is a scoping and problem formulation document that will be released for public comment when the IRIS Program formally initiates an assessment. Thus, EPA is not yet

able to discuss potential usage of existing PBPK models in the content of Agency decision making needs. However, Mn is on the IRIS 2014 Multiyear Agenda and EPA has interest in monitoring activities related to PBPK Mn research.

2. Most of the meeting time was focused on slide presentations (attached).
    - A significant portion reviewed the previously published PBPK models and analysis.
    - Sensitivity analyses of the previous models were presented, which are useful in identifying potential sources of parameter uncertainty.
    - An equation to adjust gastrointestinal (GI) uptake of dietary Mn as a function of dietary intake was presented, which is needed for evaluating exposure-dose across the human population.
    - A new rapid-association-dissociation model for Mn brain tissue equilibration was presented.
        - Uses same model structure but slides show that fits to data are improved with alternate parameters.
        - Has only been developed for the rat.
        - However, in discussion afterward Harvey Clewell (Ramboll) said that the EPA should **not** use this new model version since the long-term predictions are equivalent between the two model versions. Hence, the significance is not clear especially given that the Agency has not articulated its specific decision-making needs for an Mn assessment. Further comparisons between the models can be made based on specific scenarios which may be discussed at future meetings.
3. Discussion of model code availability.
    - Files provided to U.S. EPA staff in 2012 contain models essentially as used for all subsequent results, except rapid association-dissociation modeling. Internal model parameters have not been changed since then.
    - However, the 2012 files would not include scripts specifying input parameters (exposure control settings) for more recent analyses/papers (e.g., Gentry, et al., 2017), or equation for GI uptake vs. exposure.
    - Since results in more recent papers for human dosimetry are indicated as part of model validation, model files sufficient to reproduce those will be needed by the EPA before it could fully evaluate the models.
4. Next steps:
    - Mel Anderson offered to provide a summary of prior milestones in the development of the Mn PBPK model work.
    - Considering other priorities, EPA offered to conduct a targeted, screening level analysis of model code, focusing on several topics covered in the presentations. Following the meeting EPA developed the following list of targeted analyses and estimates it may take several months to provide feedback, depending on other Agency priorities:
        1. Evaluate form of model nonlinearity vs. data on linear-linear scale plots, to supplement current plots.
        2. Evaluate uniqueness/identifiability of model parameters vs. data (total tissue Mn) and vs. predictions (free Mn in brain).
        3. Use of adjustment factors in matching model to dosimetry data in monkeys and humans, potential setting of factors to predict dosimetry in humans for exposures where internal doses are not known.
    - All attendees agreed that additional periodic check-in meetings would be helpful, in particular as specific EPA decision-making scenarios are clarified which help frame applicability of the existing PBPK model work. EPA indicated that because Mn is not currently an active IRIS assessment, it cannot dedicate a significant amount of staff resources to providing QAAP-level feedback on the model work. Thus, future meetings

should be strategically timed, i.e., discuss feedback on the targeted, screening level analysis of code data discussed above or to occur when additional details of Agency decision-making needs can be shared to advance model applicability discussions.