Appointment

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]
Sent: 10/11/2018 7:41:40 PM
To: Thayer, Kris [thayer.kris@epa.gov]

Subject: FW: meeting to outline advances in Mn-PBPK modeling

Start: 11/16/2018 5:00:00 AM
End: 11/17/2018 5:00:00 AM
Show Time As: Free

From: Schlosser, Paul
Sent: Thursday, October 11, 2018 3:23 PM
To: Boyes, William; Jarabek, Annie; Kenyon, Elaina; Brown, James; White, Paul; Lin, Yu-Sheng; Hoyer, Marion
Cc: Bateson, Thomas; Wright, Michael; Vandenberg, John; Bussard, David; Morozov, Viktor; Thayer, Kris
Subject: FW: meeting to outline advances in Mn-PBPK modeling

EPA colleagues,

Per the emails copied below, Mel Andersen and colleagues have been working on a revision of the manganese PBPK models and would like to set up a meeting to present the work. (I will begin with an overview of the PBPK model QAPP that was finalized earlier this year, how we evaluate models for use in IRIS assessments.) Of the dates that Mel proposed, both Kris and I can make **Nov. 16 or 19**, the Friday or Monday before Thanksgiving. Also indicate if morning or afternoon is preferred. Given the agenda, we probably want 2 hours at least, I'm thinking 3 for plenty of discussion.

I would like to include as many of the scientists with 'history' on this as possible. Please let me know which of these dates you could make. Hopefully this is far enough in advance that we can include everyone, but otherwise I'll pick the best available time, rather than trying to go later in the year.

-Paul

From: Mel Andersen [mailto: Ex. 6 Personal Privacy (PP)]
Sent: Thursday, October 11, 2018 11:37 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>

Cc: Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>
Subject: Re: meeting to outline advances in Mn-PBPK modeling

Paul,

Thank you for your detailed response to my earlier letter. We would be happy to have a meeting so that you can discuss the QAPP process and that we can provide an update on the Mn PBPK models. From our side, we would have Harvey Clewell, Miyoung Yoon, Mike Taylor, Athena Keene, and me attend in person and Robinan Gentry and Cynthia Van Landingham attend via teleconference/WebEx. We welcome all members of the EPA that you mentioned to attend this initial meeting. Everyone from our team is available November 12, 14 through 16 or 19 and 20. The time can be scheduled around the availability at EPA.

We propose a draft agenda covering:

- EPA's views on the QAPP
- Background on the Mn PBPK models
- Initial rat, monkey, and human Mn PBPK models
- New work on Mn PBPK models

o Adding drinking water as a route of entry for Mn

o Developing a model with rapid tissue binding/dissociation rate constants

o Sensitivity analysis for PBPK models

We are particularly interested in input about work that needs to be done to make the PBPK models as useful as possible for an EPA risk assessment of Mn as well as what work EPA would like to see included in the sensitivity analysis.

We are prepared to provide a short document of latest adaptations in the models to date as well as a copy of all of the presentation material in advance of the meeting. The planned presentations will show some of the latest model fits to data.

On a broader note, it would be difficult for us to provide all of the data that EPA is requesting for the QAPP process in advance of this meeting. Therefore, we would be pleased to send additional data and/or schedule additional meetings once we have a better understanding of the QAPP process.

Best regards,

Mel

-----Original Message-----
From: Schlosser, Paul <Schlosser.Paul@epa.gov>
To: Mel Andersen Ex. 6 Personal Privacy (PP)
Cc: Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Mon, Oct 1, 2018 11:16 am
Subject: RE: meeting to outline advances in Mn-PBPK modeling

Hi Mel,

Cc: Kris Thayer, Tina Bahadori

Sorry it's taken a bit to get back to you. It would be good to have a meeting where I and other EPA staff can hear about your revisions of the model and have some discussion of that. Because this is something that could potentially be used in an NCEA/IRIS analysis, other EPA staff should attend (including Will Boyes, Elaina Kenyon, Annie Jarabek, and Kris Thayer), which makes scheduling a bit more difficult. We'd like to plan something for mid-November. I think that Monday-Thursday the week of Nov. 12 should work, or possibly the 19th or 20th (Monday/Tuesday of Thanksgiving week). Can you check, come back with a few specific dates and time windows in there when you and others on the modeler team would be available?

Also, you should know that all materials presented, a roster of the meeting attendees, and a summary of action items (if applicable) will be posted on the IRIS website under "stakeholder requested meetings." https://cfpub.epa.gov/ncea/iris2/events.cfm#stakeholderMeetings

Second, as you may know from Harvey and the project he's leading on chloroprene, we now have a quality assurance process plan (QAPP) that we follow in evaluating any PBPK or other type of model we might consider for use. This is an implementation of newer policies set by EPA's Office of Research and Development (ORD) regarding computational models. It also reflects experience from evaluating quite a few PBPK models for use in risk assessments and many discussions among EPA's Pharmacokinetics Workgroup (PKWG), and others. You may recall this paper on which Eva McLanahan was lead author, which was part of our evolution in this direction: https://www.ncbi.nlm.nih.gov/pubmed/22045031. A copy of the QAPP is attached.

So, the new ORD policy and the PKWG QAPP raise the bar on what is required for model use for NCEA assessments. While I know that the Mn models were developed under the oversight of EPA staff with good expertise (Will, Elaina, and Annie), that was specifically for the proposed use of MMT as a fuel additive, which was expected to result in highly soluble Mn particulate forms. To use a model in an NCEA assessment today, it will need to pass our current, more rigorous standards (QAPP) where the potential application to multiple Mn forms will likely need to be considered.

As part of our meeting, I can present an over-view of the QAPP, its primary features and requirements, with some examples of errors or issues we find and how they might be addressed. It's not just a matter of having reproducible model code and traceable parameters, but biological realism balanced by parsimony in model structure/parameters. Our hope is that over time those who are developing new models (or revising old ones) for possible use in risk assessments will be aware of and follow these standards, as it would then make our job of reviewing a model and determining applicability easier. We'd much rather review a model that is 'clean' than be trying to triage.

Frankly, I think we could have a more substantive meeting, make better use of the time if we could first get copies of the revised model workspaces and at least a draft report describing what changes were made, showing model fits to data, and any other results you plan to present. If we could get these in October, that would allow us to do an initial, if cursory review, and possibly flag some things for discussion. Preferably the workspace would have the scripts that produce the plots and tables, as checking those is part of the QA process.

Sincerely,

-Paul

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Paul M. Schlosser
NCEA, U.S. EPA
M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov

From: Mel Andersen [mailto Ex. 6 Personal Privacy (PP)
Sent: Monday, September 24, 2018 11:43 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: meeting to outline advances in Mn-PBPK modeling

Paul,
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The team developing PBPK models for manganese would very much appreciate the opportunity to schedule a meeting with you in October. The specifics about our request for a meeting and possible dates are included in the attached letter. Let me know if you have any questions and whether one of the proposed days works with your schedule.

Mel Andersen

Andersen ToxConsulting LLC

424 Granite Lake Ct

Denver, NC 28037-6531

Cell: 919-624-3705

Ex. 6 Personal Privacy (PP)