Message

From: Anitole, Katherine [Anitole.Katherine@epa.gov]
Sent: 3/12/2020 12:01:02 PM
To: Lowit, Anna [Lowit.Anna@epa.gov]
CC: Grable, Melissa [Grable.Melissa@epa.gov]; Fischer, David [Fischer.David@epa.gov]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Dawson, Jeffrey [Dawson.Jeff@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Blair, Susanna [Blair.Susanna@epa.gov]; McOliver, Cynthia [McOliver.Cynthia@epa.gov]; Pfahles-Hutchens, Andrea [Pfahles-Hutchens.Andrea@epa.gov]; Akerman, Gregory [Akerman.Gregory@epa.gov]
Subject: AGENDA: SAG Meeting, Thursday, March 12, 2020
Attachments: DRAFT_Internal MC Peer Review Meeting Minutes talking points20200302.docx; TSCA SACC Meeting Minutes and Final Report for December 2019 Meeting on EPA's Draft Risk Evaluation for N-Methylpyrrolidone; First 10 REs_Cancer MOA (3).docx; SACC Comments on the FIRST 10 DRAFT RISK EVALUATIONS.docx

All,

Apologies for the tardy delivery of this morning's agenda.

The following attachments in this email include:

1. Draft Internal MC Peer Review Meeting Minutes – just received
2. Meeting Minutes and Final SACC report for NMP – just received
3. Updated cancer MOAs for the First 10
4. Updated SACC comments regarding cancer MOA for the First 10

SAG Meeting Agenda

The following is from the RAD IO regarding SAG assistance on TSCA REs:

1. **Interfacing with the SAG: Hazard call and WOE integration for cancer MOA**
    a. Given the resources, timeline, and sheer number of REs, separate cancer assessment documents are not possible; how to do this in a timely manner for TSCA REs
    b. Input needed ASAP on development of a checklist approach and boiler plate language for:
        i. Developing a consistent/systemized/generic approach for WOE integration for cancer MOA; need to more clearly articulate our conclusions and how/why we got there; how to articulate the default approach in a generic way
        ii. Addressing the following:
            1. Do the data support a mutagenic MOA, i.e., data supporting a linear extrapolation from the point of departure?
            2. Do the data support a non-genotoxic MOA?
        iii. Includes consideration of alternative non-genotoxic MOAs
            1. Nuclear receptor/PPARα proliferation mitigated mechanism
            2. Cytotoxicity and regenerative hyperplasia
            3. Oxidative stress
            4. Immunosupression
        iv. What to do in cases where there isn't enough information to reach a firm conclusion(s) for either MOA? What is the default?
    c. ORD and OPP have differences of opinions – what is the thinking in our AA-ship
    d. All-day training as already proposed by the SAG, but the checklist and boiler plate language is of higher priority for the near term

e. Meeting with ACC to discuss MOA approaches (date TBD)

ACTION ITEM: Andrea and Kathy will develop a TD-like memo for the SAG efforts on MOA; Stan will review and provide comment; this will be sent to the SAG in time for our meeting next Thursday.

2. **Basic training (practical applications) on agency guidelines on risk assessment/risk characterization**
   a. This includes the broad spectrum: hazard ID, DR, and exposure
      i. ORD POC Emma Lavoie: Training modules (and suppl documents) that can be pulled off the shelf from ORD
      ii. ORD/RAF POCs Maria Doa & Lawrence Martin: Are there any staff that can facilitate this training?
   b. New RAF project: mega document on hazard/tox guidelines updating all of the guidelines, taking into account tox comp
   c. SAG: Could the SAG look the agency guidelines and see if there is anything they could add from our AA-ship perspective?
   d. When can the training start? Cathy suggested May, ideally

ACTION ITEM: Andrea and Kathy will reach out to ORD, the RAF, and the SAG to provide guidance and coordination of training.

3. **Other Issues**
   a. Protocols for exposure data for workers/ONUs via monitoring

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From: Anitole, Katherine
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Cc: Grable, Melissa <Grable.Melissa@epa.gov>; Fischer, David <Fischer.David@epa.gov>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Hughes, Hayley <hughes.hayley@epa.gov>; Blair, Susanna <Blair.Susanna@epa.gov>; McOliver, Cynthia <McOliver.Cynthia@epa.gov>; Pfahles-Hutchens, Andrea <Pfahles-Hutchens.Andrea@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: SAG: First 10 draft REs - WOE integration for Cancer MOA and SACC Peer Review comments

All,

Attached is the excerpted portions of the cancer WOE sections from the First 10 REs (updated from previous version) AND the consolidated comments for those cases that have completed SACC peer review.

Please note: SACC Peer Review Reports are released 90-days following the SACC meetings. Of the First 10 chemicals that have cancer endpoints *and* have gone to SACC Peer Review, only 1,4-D and 1-BP have SACC Peer Review Reports; MC went to the SACC the beginning of December 2019 (has a transcript but no SACC report); CCL_4 went to the SACC just last week and has neither a transcript nor a SACC report (but comments on InsideEPA are available). TCE, PERC, and Asbestos, all with cancer endpoints, have not yet gone to the SACC.

We can use these as a starting point for the SAG project and as a topic for discussion at our next meeting on March 9th.

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Cc: Grable, Melissa <Grable.Melissa@epa.gov>; Fischer, David <Fischer.David@epa.gov>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Hughes, Hayley <hughes.hayley@epa.gov>; Blair, Susanna <Blair.Susanna@epa.gov>; McOliver, Cynthia <McOliver.Cynthia@epa.gov>; Pfahles-Hutchens, Andrea <Pfahles-Hutchens.Andrea@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: RE: SAG Meeting on Monday 2/10

Anna,

I am not sure, but I will check and get back to you.

Also, I still need to gather the SACC comments on WOE integration for cancer MOA for the First 10. I will work on getting that to you all by early next week.

These would include the draft REs for the following cases: 1,4-D, 1-BP, and MC.

From: Lowit, Anna <Lowit.Anna@epa.gov>
Sent: Friday, February 28, 2020 9:32 AM
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Kathy

For those with PBPK models or other high quality PK data, did y'all check to see if you could make a KMD argument for any of these?

Anna

Anna B. Lowit

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Subject: RE: SAG Meeting on Monday 2/10

All,

We are expecting RAD managers to get back to us regarding their specific needs for MOA/MMOA training.

In the meantime, Andrea and I excerpted portions of the cancer WOE sections from the First 10 REs (attached) as a starting point for the SAG project (outlined below).

We can discuss this at our next meeting on March 9.

Please let me know if you have any questions.

Thanks,
Kathy.

SAG Project: WOE Integration for Cancer MOA for REs

1. Develop a consistent/systemized/generic approach for WOE integration for cancer MOA; how to articulate the default approach in a generic way?
    i. Do the data support a mutagenic MOA, i.e., data supporting a linear extrapolation from the point of departure?
    ii. Do the data support a non-genotoxic MOA?
    iii. What to do in cases where there isn't enough information to reach a firm conclusion(s) for either MOA?
    iv. Starting material:
        1. Portions of the cancer WOE sections from the First 10 REs have been merged into one table
        2. Table illustrates the differences across all 10, reinforcing the need for developing a consistent/systemized/generic approach across all REs that documents the WOE integration discussion evaluating the available genotoxicity data
2. Consideration of developing training for item (a) tailored to the specific needs of RAD and TSCA REs
3. Longer-term training needs

i. All-day training with people from outside EPA presenting the MOA and Human Relevance FWs and several case studies as group exercises, based on an existing training class

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Subject: RE: SAG Meeting on Monday 2/10

Hi Anna,

Thanks for that information – this is exactly the kind of training we need for all human health assessors in RAD. We will certainly work with you on scheduling this in the future. For the current (next 20) REs, RAD managers are asking for something more tailored to TSCA REs in order to improve consistency in the approach and evaluation of the data. I just got out of the meeting with RAD managers, and they are going to draft their specific needs for MOA/MMOA training. I don't know when we can expect to hear back from them, however, in the meantime, Andrea and I thought a good first start to improving MOA/MMOA write-ups in the REs would be to compare these narratives across the First 10 REs as well as the SACC comments pertaining to this issue. She and I will pull this information together. Our thinking is this would be a first good step for the SAG.

Thoughts?

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Sent: Thursday, February 20, 2020 9:23 AM

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Subject: Re: SAG Meeting on Monday 2/10

It will be an all day training with people from outside Epa. It will go thru the MOA and Human Relevance FWs and several case studies as group exercises. It is expected that people attend the entire day and do not leave early. This is an existing training class so little additional prep is required. There is some flexibility in when, I need some potential dates from OPPT to coordinate with the speakers.

Sent from my iPhone

On Feb 20, 2020, at 7:51 AM, Anitole, Katherine <Anitole.Katherine@epa.gov> wrote:

Anna,

Just thinking.

Can you give us an idea of what the training would look like and how soon you can get it set-up? That would help in our discussion with RAD managers.

Thanks.

From: Anitole, Katherine
Sent: Thursday, February 20, 2020 7:43 AM
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Subject: RE: SAG Meeting on Monday 2/10

Hi Anna,

We are meeting with RAD management this morning at 8:30. We will ask them your questions and hopefully have an answer sometime later today.

From: Lowit, Anna <Lowit.Anna@epa.gov>
Sent: Tuesday, February 18, 2020 9:25 AM
To: Grable, Melissa <Grable.Melissa@epa.gov>
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Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: Re: SAG Meeting on Monday 2/10

Hi everyone

I'm closing in identifying some people from outside EPA who can help give MOA training. I need to know a couple things: when do you want to do this (keep in mind, this would be an all day training)? And how many people (I suggest toxicologists and also those doing the risk characterization).

Anna

Sent from my iPhone

On Feb 6, 2020, at 10:57 AM, Grable, Melissa <Grable.Melissa@epa.gov> wrote:

Below is the agenda for our next SAG meeting on Monday 2/10. We are not planning on having a call-in number unless one is needed. Please email or call me if you need a call-in number. Thank you!

Agenda:

1. Kathy and Andrea's Detail with David: description and goals
2. Discussion of the Roadmap in guiding the purpose of the SAG
3. Request for OPP input on how they handle public/peer review/IAIA comments
    a. We are looking for suggestions on process improvements for the WP chemical program
    b. How to maintain consistency in responses across chemicals?
    c. Who makes final decisions?
    d. Is contractor support used?
    e. Any other useful information on process
4. Discussion of possible SAG project(s): Science/science policy issues flagged as having higher priority based on an OPPT/RAD survey:
    a. **Mode of Action**
        i. There is a need for developing a consistent/systemized/generic approach across all REs that documents the WOE integration discussion evaluating the available genotoxicity data
        ii. Do the data support a mutagenic MOA, i.e., data supporting a linear extrapolation from the point of departure?
        iii. Do the data support a non-genotoxic MOA?
        iv. What to do in cases where there isn't enough information to reach a firm conclusion(s) for either MOA?
        v. How to articulate the default approach for all of these in a generic way?
    b. **Benchmarks for Cancer IUR** (10^{-4} for workers vs. 10^{-6} for general population)

i. Discuss what guidance and context there is for consideration of the cancer risk estimates for benchmarks for risk management

Thanks,
Melissa

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