Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 11/12/2019 2:05:03 PM
To: Robinan Gentry [rgentry@ramboll.com]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]
CC: Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Cascio, Wayne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a1bd931ca2f84ea8ac2f4c44538f3589-Cascio, Wayne]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Dunlap, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=591eb15a268249dda0c05a7451f765c3-Dunlap, Dav]; Walsh, Patrick [patrick-walsh@denka-pe.com]
Subject: RE: Chloroprene PBPK: Peer review charge questions

Robinan, all,

FYI, I have been emailing with Jerry Campbell (and he talking with Harvey) re. some details of the model code/scripts as I've been working on the QA. None of these have been major, but a couple of figures will have minor or modest changes. I thought it would be OK to not copy everyone on those technical details.

I think there are only a few pieces left for me to check, and I will plan to complete the review by Nov 21. It's possible I can finish ahead of that. The biggest possible change is if a trachea-bronchial tissue compartment were to be created. That doesn't impact the current QA, but I'd need to do a targeted review of such a change.

Best regards,
-Paul

From: Robinan Gentry <rgentry@ramboll.com>
Sent: Friday, November 08, 2019 3:51 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Dunlap, David <dunlap.david@epa.gov>; Walsh, Patrick <patrick-walsh@denka-pe.com>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Paul,

Thank you for providing this feedback to consider as we finalize the documentation of the Ramboll PBPK model for the EPA peer review. We are currently reviewing the comments you provided and are considering how they can be addressed. We plan to provide a detailed response to address each comment by Friday, November 15. We would also request a date for completion of the QA process of the model so we can provide the final documentation for peer review as soon as possible.

In the interim, if there are any other questions or comments, please do not hesitate to let me know.

Best,
Robinan

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Thursday, November 07, 2019 7:43 AM
To: Robinan Gentry <rgentry@ramboll.com>; Vandenberg, John <Vandenberg.John@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Dunlap, David <dunlap.david@epa.gov>; Walsh, Patrick <patrick-walsh@denka-pe.com>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Robinan,

Thanks for forwarding your comments on the EPA charge questions. It helped clarify that until we complete the model QA, some of our perspectives may be difficult to convey. While we proceed with completing the QA however, we wanted to provide some additional feedback for clarification and to provide Ramboll the opportunity to enhance the model elements and model documentation before we proceed with peer review. EPA will update (and augment, if necessary) the charge questions after completing the QA.

Background
EPA modelers and statisticians believe there is much greater uncertainty associated with this model than those previously used due to the minimal *in vivo* PK data available for chloroprene, which is the reason the model wasn't used in the initial assessment. We will provide a more detailed description of EPA's prior uses of IVIVE, and the *in vivo* PK data available for those chemicals, as part of the background material to the peer reviewers. Normally the submission of an EPA product for external review carries the implied message that EPA fully endorses the product. The Ramboll PBPK model has *not* fully passed our normal internal review process, so to an extent the charge will continue to convey EPA's uncertainty.

Question of uncertainty in IVIVE as described in the background: While we will acknowledge the simplicity and chemical domain of the modeling presented by Wambaugh et al. (2015), it is to the best of our knowledge the only study that has extensively evaluated the uncertainty of IVIVE for compounds of toxicological interest (vs. pharmaceuticals). At steady-state, PBPK model predictions only depend on a limited set of parameters and can therefore be reasonably represented with simpler forms; this does not invalidate the conclusions from them. We will cite the Yoon et al. (2012) review paper you suggested, noting that Table 4 in that paper supports our general conclusion about the uncertainty of IVIVE, and in fact shows some compounds where the IVIVE prediction is more than an order of magnitude in error.

Regarding the MCMC analysis and statistical evaluation of data with repeated measures, and footnote 1: The EPA originally conveyed this issue to Denka in the document, "Attachment 2: Systematic Review of Chloroprene [CASRN 126-99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC)", Table 6 (January 2018). The issue was mentioned in at least one email, sent Friday, May 31, subject "RE: chloroprene – Bayesian analysis", and was raised towards the end of our last in-person meeting. Hence, EPA believes it has provided sufficient prior opportunity for Denka and Ramboll scientists to engage us on this issue. In creating the draft charge, EPA was envisioning that only central estimates of parameter values for the Ramboll/Denka model would be utilized, as is usually done in EPA risk assessments. In part this choice was made because EPA has concerns about the interval estimates provided by Ramboll/Denka. Given that Ramboll/Denka have expressed that they believe the interval estimates are sound, specific input from the peer reviewers will be sought on this matter.

Specifically, since Ramboll's comments on the draft charge indicate their belief that the analysis is sound, the EPA will proceed by removing the footnote, but instead add charge questions to address the soundness of these values and their potential application. We understand from the comments that Ramboll considers those to be estimates of uncertainty in the population mean, not interindividual variability. The primary question will be whether the reported confidence intervals are sound measures of uncertainty in the population mean parameter values. A negative response on this question will not necessarily be interpreted as invalidating the model's ability to predict population average behavior, but it will negate the possibility of using the reported confidence intervals to evaluate uncertainty in these predictions. (A separate question asks if the reported mean parameters provide sound predictions of population-average PK, which is critical to use of the model.)

The EPA notes that, while Ramboll has stated its belief that the current level of documentation of the MCMC analysis in the report is adequate, EPA believes that peer reviewers with statistical expertise will expect more thorough documentation. We suggest that a complete description of an MCMC analysis should include:

1. A more thorough description of the data, including the number of animals or human donors from which each set of pooled microsomes was created, and an explanation of the repeat sampling involved ("repeated measures"), and number of independent experimental replicates. Most of this information is not in the current draft.
2. A list of the parameters being estimated and a full description of the prior function with justification for the choice. (The current draft appears sufficient, but we include this statement here for completeness.)
3. A complete prose description of the likelihood function, including a formula and justification for the form. (This is not in the current draft.)
4. A full description of convergence criteria and method of implementation, perhaps with some graphical demonstration of convergence results. While the criteria used may be adequate and may be satisfied according to the analysis, the question, in part, is how well an external reviewer can discern that from the material provided. For example, Ramboll's comments on the draft charge state specifically that the method of Gelman was used (gelman.diag routine in the R package CODA), but these details and citation of Gelman are not provided in Supplemental Material B. (Note: we believe that Gelman recommends a CSRF threshold of 1.1, rather than 1.2, but use of 1.2 *may* be sufficient. If 1.2 is used, rationale for deviating from Gelman's proposed threshold (1.1) should be given.) While full analysis outputs were provided in Supplemental Material D, is this the manner in which you wish to convey results to an external reviewer? One might also show, for example, covariance plots for Vmax vs. Km.
5. A formal statement of the interpretation of the distributional parameter estimates that resulted from application of MCMC; e.g., that these are measures of uncertainty in the population mean values.

These additions will help external reviewers in evaluating the associated charge questions.

Somewhat separately, since the alternative approach is ultimately used to estimate human lung oxidation, it would be helpful to see how the resulting predictions for the *in vitro* PK model compare to the corresponding human lung microsome incubation data; i.e., to show visually the extent to which the predicted human lung metabolism exceeds the observed rate of CP decline in the system.

Coincidence of charge questions re. IVIVE calculations in the Ramboll model and EPA's 1-CEO clearance analysis: Since the IVIVE calculations used by Ramboll and those used by EPA for 1-CEO clearance are "parallel" calculations, based on the same or comparable underlying assumptions, we believe it is appropriate if not imperative to consider them together. For example, if reviewers believe that different values should be used for the tissue concentrations of microsomal protein, the comment would apply equally to where it is used in both the PBPK model and the 1-CEO analysis.

Perfusion rate (and tissue volume) used to evaluate 1-CEO clearance in lung:
In Ramboll's comments a concern is noted that in the analysis of 1-CEO clearance, the total lung tissue volume and perfusion rate are used, but the processes of 1-CEO production and elimination are expected to be confined to the tracheobronchial (TB) region, hence that it would be more accurate to use the TB-specific tissue volume and perfusion rate. The comments also state that the Ramboll model uses the arterial blood concentration (Ca) to calculate the rate of CP metabolism. To be clear on this matter, lines 134, 156 and 164-165 from the chloroprene.model file are as follows:

134: CVLU = ALU/(VLU*PLU) ;
156: RAMLU = VMAXLU*CVLU/(KMLU + CVLU) + KFLU*CVLU ;
164: RALU = QC*(CPU-CVLU) - RAMLU ;
165: dt(ALU) = RALU ;

This is a standard model structure for calculating the amount of a compound in a tissue with metabolic elimination, and the concentration in venous blood exiting the tissue (hence the annotation "CVLU"), which the EPA considers generally reasonable. Because of the PBPK model structure, Ca is identical to CVLU. But this model structure assumes a lung tissue concentration of CP at equilibrium with the exiting blood and that CP is cleared from lung tissue with a clearance rate = ALU*QC/(VLU*PLU); the perfusion rate used for the lung tissue is total cardiac output (QC) and the tissue volume VLU is calculated from the fraction of total lung volume (VLUC) from Brown et al. (1997). The analysis of 1-CEO clearance for the lung uses the same tissue volume and total blood perfusion as is used in the Ramboll PBPK model. EPA believes that either both are acceptable approximations of biological reality, or both should be revised.

EPA's initial judgment was that both the Ramboll model and the current analysis of 1-CEO clearance are acceptable approximations for the purpose of calculating the relative intensity of 1-CEO metabolism in human and animal lung tissue. But it is possible, and perhaps likely, that external reviewers will reach the same conclusion as expressed in Ramboll's comments regarding the 1-CEO clearance analysis: TB-specific values for tissue volume and perfusion should be used. However, EPA will interpret that as indicating that the model parameters (and structure) for the parent CP PBPK model likewise need to be revised, so the dosimetry of CP and its metabolic rate in lung tissue are calculated using identical values for blood flow and tissue volume as is used in evaluating the clearance of 1-CEO. Hence, it might be preferable to make these revisions ahead of external review; i.e., Ramboll can revise its model to set the tissue volume and perfusion rate for the metabolizing portion of the lung to just represent the TB region, and EPA will revise its analysis of 1-CEO clearance accordingly. Note that such a revision will involve revising the model structure and diagram (Figure 1) in the Ramboll report and adding a separate compartment for the TB tissue. The IVIVE calculations for CP will also need to be revised, since the tissue samples used in vitro were homogenates of whole lung tissue, so a factor to account for the dilution of TB-associated metabolism by non-metabolizing lung tissue will need to be incorporated.

Estimation of 1-CEO Clearance in Liver and Lung

Ramboll is correct that the analysis may not apply to 2-CEO. However, it is possible that the reaction rate of 2-CEO, while more rapid than 1-CEO, still differs between rodents and humans. This is a matter that will be evaluated (and a question that may be put to external reviewers) only if EPA determines that use of the PBPK model is appropriate. EPA does note, however, that one cannot explain the observation of rodent tumors occurring outside of the metabolizing tissues (e.g., mammary tumors) if the model effectively assumes that a metabolite that is too reactive to escape the tissues in which it is formed is the causative agent.

Sincerely,
-Paul

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To: Vandenberg, John <Vandenberg.John@epa.gov>
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Subject: RE: Chloroprene PBPK: Peer review charge questions

John,

Attached please find a document summarizing Ramboll's comments on the draft charge peer review of the Ramboll (2019) Chloroprene PBPK model. While we greatly appreciate USEPA's efforts to work with us to ensure the development of a PBPK model that is scientifically sound, we have significant concerns regarding the current draft of the charge for the external peer review of our model. Our concerns include:

1. Content and format of the draft charge that is inconsistent with the USEPA Peer Review Handbook (2015) and similar charges for USEPA peer reviews;
2. Presentation of USEPA opinions as fact in the Background to the draft charge questions that may introduce bias and in some cases are incorrect;
3. Inclusion of the USEPA (2019) 1-CEO Clearance Analysis as a component of the charge to the peer review in the absence of clearly providing the relevance of this analysis to the evaluation of the Ramboll (2019) PBPK model. Further, in our review of the USEPA (2019) Analysis, we identified discrepancies that significantly impact any results or conclusions that may be drawn based on this analysis.

Because of these concerns and the identification of potential errors, we are requesting that USEPA revise the draft Charge for the peer review of the Ramboll (2019) Chloroprene PBPK model, as well as the USEPA (2019) 1-CEO Clearance Analysis. Further, we would also request time to review the revised charge and any revisions to the USEPA (2019) 1-CEO Clearance Analysis and provide recommendations as appropriate prior to USEPA finalizing these documents and providing them to the peer reviewers.

After you have had time to review our comments, if you have any questions, please feel free to contact me.

Thanks,
Robinan

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From: Walsh, Patrick <patrick-walsh@denka-pe.com>
Sent: Thursday, October 17, 2019 11:10 AM
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Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Schlosser, Paul <schlosser.paul@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Dunlap, David <dunlap.david@epa.gov>; Robinan Gentry <rgentry@ramboll.com>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Hello John,

A quick update:

Ramboll has been hard at work on their detailed response to the peer review charge questions. They expect to be complete well within our revised timeframe. Robinan Gentry of Ramboll will send the comments to this group tomorrow before close of business. Thanks for your patience and for including us in this process.

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From: Vandenberg, John <Vandenberg.John@epa.gov>
Sent: Thursday, October 10, 2019 8:02 AM
To: Walsh, Patrick <patrick-walsh@denka-pe.com>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Dunlap, David <dunlap.david@epa.gov>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Hi Patrick,

Thank you for letting me know the status of your review - we had thought from your email last Thursday that a week was adequate time. We don't want to have any delays moving forward with the peer review but it seems you have comments that we would like to consider, so we agree to wait another 9 days. Please let us know if you have any comments as they are available.

In addition, it seems some changes are being made to your report to make corrections and add clarifications as indicated in recent emails between EPA and your contractors. Any discrepancies need to be resolved before sending the materials for peer review so please use this time to recheck and update your report to avoid delays.

Thank you,
John

From: Walsh, Patrick <patrick-walsh@denka-pe.com>
Sent: Wednesday, October 09, 2019 4:54 PM
To: Vandenberg, John <Vandenberg.John@epa.gov>
Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Dunlap, David <dunlap.david@epa.gov>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Hi John,

We need more time for us to provide recommendations regarding the chloroprene PBPK model peer review charge questions you sent me last Wednesday. There are 3 reasons for this request:

1. One of our experts, Mel Andersen, had a previous engagement that could not be moved and he has not been able to contribute to the effort. That commitment ends today and he is travelling tomorrow.
2. We need time to review the new clearance report because of the way it is being used to frame charge questions.
3. We have grave concerns that the manner in which certain information is presented will bias the reviewers inappropriately, and we need more time to ensure that we assemble a cogent and helpful set of recommendations to ensure the most objective review possible.

To that end, I'm requesting a little more time—can we submit our recommendations to you by close of business Friday, 10/18?

Thanks

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Sent: Wednesday, October 2, 2019 3:46 PM
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Cc: Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>
Subject: Chloroprene PBPK: Peer review charge questions
Importance: High

Patrick,

We've been diligently evaluating the Ramboll report and conducting analyses related to physiologically-based pharmacokinetic parameters and modeling of chloroprene (references below).

We are moving forward to arrange through a contractor an independent letter peer review by appropriate experts.

In addition to the Ramboll report, we are providing an EPA analysis that we wish to have peer reviewed.

Per our discussion early this summer, we are providing for your information the attached draft Charge questions that will be addressed by the peer reviewers, plus an EPA analysis that we have developed.

Please let us know within a week (by next Wednesday) if you have any major comments on the Charge questions. We are not seeking any comments on the EPA analysis.

Thank you,

John

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References:

Ramboll. (2019). Incorporation of in vitro metabolism data in a physiologically based pharmacokinetic (PBPK) model for chloroprene.
U.S. EPA. (2019). In Vitro to In Vivo Extrapolation (IVIVE) of Metabolism and Non-Enzymatic Conjugation of (1-chloroethenyl)oxirane (1-CEO) and Estimation of Total 1-CEO Clearance in the Liver and Lung of Mice, Rats, and Humans.