April 4, 2014

ACC Formaldehyde Panel
Specific Recommendations for Workshop Agenda

In addition to the comments provided in the cover e-mail, the ACC Formaldehyde Panel has some specific recommendations to the charge questions to help insure that the dialogue will be useful in informing the assessment. [*suggested new or reframed questions are in italics*]

1. Session 1 (toxicokinetics and endogenous).

    a. Under (1) when asking "To what degree, and in what form, is endogenously produced formaldehyde available to react with cellular macromolecules in various tissue compartments?" it would be helpful to add a question asking: *"What role does or should the presence of endogenous formaldehyde play in the development of a relevant dose metric?"* This would help put the discussion in the context of decisions the agency must make for the assessment.

    b. Under (2), while EPA asks about the "implications of uncertainties regarding measurements of formaldehyde and its adducts on comparing endogenous levels with the internal dose due to exogenous exposure?", it may be first helpful to simply have a discussion that asks "*what are the uncertainties*".

    c. Under (2) while EPA asks about 'notable issues' that may arise in interpreting the exogenous and endogenous adducts, and their use as internal dose metrics, it may be helpful to include a few more questions that will provide EPA and stakeholders with more specific advice regarding the dose metric. We suggest:
        i. *What does the available toxicokinetic data for formaldehyde suggest could be the relevant dose metric for evaluating the potential for LHP cancers?*
        ii. *What are other the remaining uncertainties in the toxicokinetics related to target tissue dosimetry for LHP cancers?*

    d. In this discussion it would be helpful to also ask the following question to help inform how the endogenous issue could be captured in the BBDR model:
        i. *Can the available Biologically Based Dose-Response (BBDR) model be applied to incorporate the presence of endogenous formaldehyde in the*

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estimation of the relevant portal of entry dose metric and the potential estimates for systemic delivery?

2. Session 2: Mechanistic

   a. The 1st question here ("What mechanistic events that have been associated with the pathogenesis of LHP cancers following environmental exposures may be relevant to formaldehyde-mediated effects?") has a bias in that it is framed to only ask about positive data. We suggest that this question be reframed more neutrally, to allow for the consideration of ***all*** available data. Please consider, in place of question 1:
      i. *What are the proposed mechanisms by which formaldehyde may cause LHP cancers following environmental exposures?*
      ii. *What is the scientific evidence that supports or refutes these mechanisms or modes of action and what are their uncertainties?* (Note there was a recent NIEHS poster at SOT that showed preliminary negative findings in susceptible mice strains. It may be helpful to include discussion on this. The NIEHS lead is Dan Morgan).
      iii. *What endpoints and assays are most appropriate for assessing the potential risk for LHP cancers in humans? Please suggest those that are relevant to short term and long term research.*

   b. Regarding the 2nd question in this section, it would also be helpful add a few questions, similar to those above, regarding systemic distribution of formaldehyde. After EPA asks "Does formaldehyde need to be systemically distributed to affect the incidence of LHPs? If not, what are the most plausible alternative mechanisms?", we suggest adding:
      i. *What is the scientific evidence that supports or refutes these plausible alternative mechanisms and what are their uncertainties?*

3. Session 3: Epidemiology

   a. In addition to seeing the workshop start with this section, for question (1), it may be helpful for EPA to ask reviewers to comment on the specific different approaches EPA is asking about. Right now this is unclear. In addition to commenting on the approaches EPA presents, it may be helpful to add the following:
      i. *Please describe any other suggestions for approaches that could be used to evaluate the weight of epidemiological evidence (considering all studies and their quality as appropriate) for different LHP cancers.*
      ii. *If combinations of cancers are considered in the weight-of-evidence evaluations of causal relationships (such as with LHP cancers), is there a*

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biological basis for these combinations? How should evaluations reflect the differences and uncertainties associated with specific LHP cancer subtypes? (this last question is moved up from question 2)

b. For question (2), in regards to exposure metrics reported, we suggest the following more specific questions:
   i. *What are the uncertainties in the characterization of exposure from epidemiological studies?*
   ii. *What is the most appropriate exposure metric for evaluating the potential association of LHP cancers with formaldehyde exposure? Is this exposure metric appropriate for use in standard dose-response modeling? How should the results be interpreted in terms of the exposure metrics reported?*

4. Session 4: Integrating Evidence

   a. This important session could be framed around a discussion of the confidence in each of the evidence streams and how they do or do not support the hypothesis that environmental exposures to formaldehyde cause LHP cancers in humans. We have framed the questions below using the hypothesis based WOE approach where the same question is asked from both the negative and positive direction. Questions to guide the discussion could include:
      i. *What does the integration of the available evidence suggest regarding the association between formaldehyde and LHP cancers? Please comment on hoe the animal and mechanistic data affects the interpretation of the plausibility of the human findings.*
      ii. *What are the data/evidence that support the finding that there is an association between formaldehyde and LHP cancers? In regards to each data stream, what are the assumptions that must be made to support this association?*
      iii. *What are the data/evidence that do not support the finding that there is an association between formaldehyde and LHP cancers? What are the assumptions that must be made to support this lack of association?*

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