September 13, 2012

Via e-mail: emantus@nas.edu

Dr. Ellen Mantus
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Dear Dr. Mantus:

The American Chemistry Council (ACC) and its Center for Advancing Risk Assessment Science and Policy (ARASP) appreciate this opportunity to provide information to the National Research Council Committee (Committee) reviewing EPA's Integrated Risk Information System (IRIS) process. ACC has been actively engaged in reviewing as well as providing scientific information into IRIS chemical assessments since the inception of the IRIS program in the early 1980s. Moreover, ACC continues to advocate for significant IRIS improvements to ensure that it is a model of objectivity, transparency, and scientific accuracy. Thus, ACC has a keen interest in the important work of the Committee.

The Committee has the critically important task of assessing the scientific, technical, and process changes being implemented by EPA to its IRIS program. The Committee also will recommend modifications or additional changes as appropriate to improve the scientific and technical performance of the IRIS program. Because several reviews of IRIS assessments have identified concerns about EPA's weight-of-evidence analyses, the Committee will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.

This letter describes several re-occurring concerns as well as practical solutions for the Committee's consideration as it begins its task. We are confident that the Committee will be able to assist EPA in implementing a new and improved approach to developing IRIS assessments that uses the best available scientific information regarding hazard and exposure; employs consistent, objective methods and models; utilizes transparent evaluation procedures for data quality, cause and effect; and weighs the full body of scientific evidence.

Scientific Evaluation Improvements

EPA has initiated a multiyear, phased-in approach to implement the recommendations from Chapter 7 of the 2011 NAS formaldehyde report. Thus, numerous recommendations remain to be addressed. For example, in two recently released draft IRIS assessments (ammonia and

trimethylbenzenes), EPA has yet to make critically important changes that are needed to improve the evaluation of studies and the weight-of-evidence (WoE) evaluation of the existing literature. As described below, we recommend a two-step process for the systematic review of scientific information used for an IRIS assessment. (See, for example, Schunemann H, et. al., J Epidemiol Community Health 2011, 65:392-395; Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011), available from www.cochrane-handbook.org; and the Institute of Medicine 2011 report: Adverse Effects of Vaccines: Evidence and Causality).

Step One: Data Evaluation

Even in the most recent IRIS assessments, EPA does not set forth the criteria that it will use to evaluate studies. The data evaluation steps in IRIS assessments, therefore, appear ad hoc. Step one should include the development and use of clear criteria that the agency will employ to systematically evaluate each study. In addition to developing a formal protocol for each IRIS assessment that should include the literature search strategy and study inclusion/exclusion criteria, EPA should develop and follow a transparent, systematic approach when evaluating each individual study for quality, reliability and relevance. Standard evaluation procedures could be developed for each type of study generally evaluated by the IRIS program (including *in vivo*, *in vitro* and epidemiological studies).

Step Two: Weight of Evidence Integration and Synthesis

EPA should specify and implement a framework and methods that will be used to conduct the WoE evaluation to integrate results across studies. The WoE framework should give the greatest weight to information from the most relevant and highest quality studies, identified in step one. Those studies should be clearly noted in the assessment. EPA should also include and specify methods to be used to analyze individual studies for dose response of reported effects.

Simply generating a catalogue of hazards irrespective of dose and mode of action (MoA) information is out of step with our growing knowledge of how chemicals act in the body at environmentally relevant exposures. EPA's WoE approach, therefore, must consider and integrate knowledge of biological processes, MoA, and an understanding of kinetics and dynamics at environmentally relevant exposure levels within a framework that also reflects our understanding of how the level of exposure plays a role in determining whether or not there are only mild adaptive responses or alterations in biological function. A more integrated approach should also help prevent identification of risks at levels endogenously produced or routinely encountered in the ambient environment. (See, for example, the 2011 NAS formaldehyde report).

Toward Constructive Solutions

ACC's ARASP has sponsored a project that considers and summarizes data evaluation procedures used by various organizations (e.g., OECD, REACH, EPA OPPT and OPP, ECVAM, Klimisch,) for *in vitro* and *in vivo* studies. Over the next few months, ARASP will synthesize the findings and develop a white paper and manuscript, which will highlight the best practices in the field today. In addition, ARASP is sponsoring a project, slated for completion this fall, which summarizes the various WoE frameworks relevant to chemical risk assessment. The findings of this WoE project will be synthesized into a white paper and manuscript that will also highlight the best practices in the field today. ACC will share both of these manuscripts with EPA and the Committee for their consideration in developing a WoE framework.

Procedural Improvements to Strengthen the Overall Scientific Assessment

We believe that some practical changes to the current IRIS development process, as we currently understand it, could significantly improve the scientific basis of IRIS assessments.

Improving Data Acquisition through Early Engagement

Currently, there is a lack of early engagement with the scientific community, internal Agency stakeholders and the public. For instance, recent IRIS assessments (e.g., hexane, n-butanol and trimethylbenzenes) did not consider data that had been relied upon by other EPA program offices in their chemical assessments. Similarly, the timelines for developing chemical evaluations by EPA program offices are discordant and seemingly inefficient. For instance, it is not clear how the timelines for EPA's Office of Pollution Prevention and Toxics (OPPT) work plan assessments juxtapose with planned IRIS assessments or why OPPT evaluates the same chemicals that the IRIS program has evaluated.

As part of an early engagement process EPA could distribute an overarching plan for conducting the IRIS assessment to stakeholders. This plan could include the key points EPA wants to address in the assessment and would describe the data acquisition plan, data evaluation procedures, the methods to be used for dose response, and the frameworks for evaluating MoA and WoE. By allowing stakeholder review and comment at this early stage, EPA could become aware of studies underway that directly inform the assessment and stakeholders could become aware of data needs that address assumptions or uncertainties. Incorporating more information from data generators, experts, and diverse stakeholders at the outset of an assessment will lessen the need for multiple revisions of an assessment.

Improving Science through Robust Peer Review and Oversight

At present, there is no third party to oversee and ensure that IRIS assessments adequately incorporate peer reviewers' recommendations and public comments. Currently, EPA staff, who author the assessment, determine the final disposition of these recommendations. This has

proven problematic, as legitimate scientific concerns are not addressed but continue to be raised by peer reviewers, significantly delaying the release of a final assessment. For example, after two SAB reviews and an NAS review, EPA's draft dioxin assessment still has failed to implement peer review and public recommendations to provide non-linear cancer modeling.

Regarding peer review, procedures should be improved to ensure that both the selection of reviewers and the development of charge questions posed to reviewers allow for public input. The peer review process should also facilitate robust scientific exchange by the peer reviewers that includes adequate consideration of public comments and input by outside scientific experts.

Broadening Perspectives on Peer Review Committees

First and foremost, peer reviewers should be selected to serve on peer review committees based upon their expertise appropriate to the subject matter under review. The NAS, for example, is obligated to "make its best efforts to ensure that … (B) the committee membership is fairly balanced as determined by the Academy to be appropriate for the functions to be performed…."[1] ACC believes that scientists or consultants with a diverse set of perspectives, including those from industry, should be appointed to expert review committees "not because such individuals are 'representatives' of industrial …interests" but because such individuals are "vital to achieving an informed, comprehensive, and authoritative understanding and analysis of the specific problems and potential solutions to be considered by the committee."[2]

Selecting a peer review panel that includes a diverse set of perspectives is important for reviewing individual IRIS assessments and the IRIS program as a whole. Including scientists and consultants who have experience in applying the information generated from the IRIS program and reviewing individual IRIS assessments, in particular, can bring unique experience to bear on the peer review process. We understand that the Committee will discuss the question of membership in its upcoming meeting. We encourage that discussion because the issue is as relevant to the Committee's deliberations as it is to systematic review of specific IRIS assessments.

Incorporation of Further Improvements to the IRIS Preamble and Data Presentation

IRIS assessments need to "describe more fully the methods of the assessment…." Significantly enhancing the clarity of assessments will assist all stakeholders who rely on them and will enable rigorous peer review.

[1] Federal Advisory Committee Act, Section 15(b)(1).

[2] NAS Policy on Committee Composition and Balance and Conflicts of Interest, p. 3. The NAS Policy uses the term "industrial." For purposes of these comments, ACC views the terms "industry" and "industrial" as synonymous.

The New IRIS Preamble

In response to the NAS recommendation in Chapter 7 of its report on the formaldehyde IRIS assessment, EPA has replaced Chapter 1 of new IRIS assessments with a standard "Preamble that will describe the application of existing EPA guidance and the methods and criteria used in developing the assessments."[3] Two recent IRIS assessments, ammonia and trimethylbenzenes, which according to EPA "represent a major advancement in implementing the short-term NRC recommendations …," include the new Preamble.[4] EPA uses the term "preamble" intentionally "to emphasize that these methods and criteria are being applied consistently across IRIS assessments."[5] The Preamble includes discussion on: identifying and selecting pertinent studies; evaluating the quality of individual studies; weighing the overall evidence of each effect; selecting studies for derivation of toxicity values; and deriving toxicity values.

As currently written, however, the Preamble offers an abbreviated view of EPA policies, guidance documents and standard practices and fails to describe *how* the Agency conducts consistent systematic reviews or weighs the scientific information for inclusion in the specific IRIS assessment. The appended comments on EPA's draft ammonia IRIS assessment provide numerous specific examples where the language in the Preamble is not clear and/or may leave readers, including peer reviewers, with an incomplete understanding of EPA guidance and approaches to hazard identification. (See Appendices A and B.) The appended comments also offer recommendations for improvement.

EPA Evidence Tables

Recent IRIS assessments also include evidence tables of the key study findings that support an IRIS assessment and forgo the need to develop long narratives on studies. We welcome a streamlined format, such as evidence tables, to more clearly present and describe studies. EPA's recent implementation of these new evidence tables, however, could be improved. In commenting on the draft ammonia assessment, ARASP offered a number of suggested improvements. (See Appendix A, and Dr. Ted Simon's presentation on the inadequacy of the data table format made during the EPA listening session on the draft ammonia IRIS assessment (Appendix B)). Specifically, evidence tables should clearly describe EPA's ranking of study quality and how design and methodological study aspects increase or decrease the weight given to any given study; include statistical information; and present mode of action data in a manner that would support the applicable weight-of-evidence framework.

[3] USEPA, EPA's Integrated Risk Information System Program, Progress Report and Report to Congress, 2012.

[4] Id.

[5] Id.

Complete Presentation of Scientific Information

There are steps EPA can take during the development of an IRIS assessment that will help streamline the IRIS process while providing enhanced information to users and stakeholders. For instance, EPA most often presents results using a single modeling approach. Frequently, expert reviewers, including SAB and NAS, request that EPA consider alternative modeling approaches (e.g., Libby asbestos, dioxin, and formaldehyde IRIS assessments), which prompts EPA to conduct new analyses. If EPA were to present more decision points, and more analyses representing scientifically supported alternative modeling approaches before the draft is released, EPA would likely be able to finalize assessments more rapidly.

The Committee's review should include careful consideration of the end product of assessments conducted under the IRIS program. While often preferred by some risk managers, the derivation of point estimates for reference doses and cancer potencies suggests a level of scientific certainty that rarely, if ever, exists and these point estimates also incorporate a number of policy considerations. IRIS assessments, therefore, should present the range of estimates corresponding to the variety of potential assumptions and end points. Similarly, many experts have noted that due to inherent uncertainties, presentation of a single estimate may be misleading and provide a false sense of precision. (See, for example, NAS Models in Environmental Regulatory Decision Making, 2007 and NAS Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget, 2007). However, when confronted with such a risk range, decision makers in the program offices and state agencies may likely feel overwhelmed and select the lowest (most conservative) value - regardless of its probability. We encourage the Committee to provide EPA with recommendations to improve the presentation of information in a manner which takes into account, and transparently describes, inherent uncertainties as well as the range of plausible values. It is critically important that this information be presented in a manner useful to a diverse group of stakeholders.

We look forward to attending and participating in the open session scheduled for September 17, 2012 and appreciate you sharing our letter with the Committee members. Please contact either Dr. Kimberly Wise at Kimberly_Wise@americanchemistry.com, or Dr. Rick Becker at Rick_Becker@americanchemistry.com, with any questions regarding this submission.

Sincerely,

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Attachments:
Appendix A: ARASP Comments on EPA's Draft Toxicological Review of Ammonia
Appendix B: Dr. Ted Simon, Comments on Tables, Figures and Other Presentation Details in EPA's Draft Toxicological Review of Ammonia