Re: Suggestions for the Recommendations on the National Research Council Review of the IRIS Process

Dear Dr. Olden,

The American Chemistry Council (ACC)\(^1\) appreciates the considerable National Center for Environmental Assessment (NCEA) effort for a workshop on the May 2014 National Research Council (NRC) report on the IRIS process.

We welcome EPA’s leadership in organizing this workshop. To ensure the success of the workshop, we strongly recommend that EPA ensure a transparent and systematic approach to addressing the NRC report and its important recommendations. Although the agenda for the October workshop addresses three important topics, the NRC has made recommendations in six discrete areas, including over 30 distinct recommendations, including 14 high priority recommendations.\(^2\) The NRC report urges the EPA to address the high priority recommendations first and to develop a timetable for the other recommendations.\(^3\)

ACC supports the approach recommended by the NRC. In our view, it would be helpful if EPA adopts a timetable for implementing all recommendations, including the high priorities. This approach will provide a useful planning tool to EPA, and will also allow for timely and

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1 The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people’s lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.

2 High priority recommendations are listed as an attachment to this letter.

3 See NRC report at page 130.
constructive stakeholder engagement. Without a public plan, it will not be clear what topics and recommendations EPA is addressing and the expected timeline for the effort.

We recognize that EPA is addressing some recommendations in the context of chemical specific documents that are prepared for and addressed during bi-monthly IRIS meetings. While this approach does allow for some dialogue, it does not provide for robust discussions on the specific structural changes that EPA is considering. The approach also does not provide for responses to stakeholder input.

Unfortunately, it appears that EPA may not be interested in taking comments on these reforms at the bi-monthly scientific meetings. Indeed, at the most recent bi-monthly meeting, Dr. Cogliano confirmed that EPA is focusing on input on the specific science questions that EPA is interested in discussing. Public input on the structural and methodological approaches is not treated as a priority or as highly valuable. In my view, a more formal, transparent public discussion on the structural and methodological modifications would be useful. If EPA were to provide a timetable and an outline for plans to address the recommendations, including preliminary thoughts on the approaches, stakeholders would then be able to engage in discussions that are timely and relevant while contributing to the bi-monthly scientific discussions.

I appreciate your consideration of these suggestions and would be happy to meet with you and your staff to discuss them. Like you, I share a goal of seeing meaningful improvements in the IRIS program and believe these improvements can be realized quickly and efficiently. Please feel free to contact me by phone (202-249-6400) or by email (mike_walls@americanchemistry.com) with any questions.

Sincerely,

Michael P. Walls
Vice President
Regulatory & Technical Affairs

cc: Lek Kadeli, EPA
    Vince Cogliano, EPA

Attachment A: NRC High Priority Recommendations

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4 EPA does not provide for specific discussion questions that address these structural and methodological changes.
Attachment A: NRC High Priority Recommendations

General Process Issues:
- EPA needs to complete the changes in the IRIS process that are in response to the recommendations in the NRC formaldehyde report and specifically complete documents, such as the draft handbook, that provide detailed guidance for developing IRIS assessments. When those changes and the detailed guidance, such as the draft handbook, have been completed, there should be an independent and comprehensive review that evaluates how well EPA has implemented all the new guidance. The present committee is completing its report while those revisions are still in progress.

- EPA should provide a quality-management plan that includes clear methods for continuing assessments of the quality of the process. The roles of the various internal entities involved in the process, such as the chemical-assessment support teams, should be described. The assessments should be used to improve the overall process and the performance of EPA staff and contractors.

Problem Formulation and Protocol Development:
- EPA should establish a transparent process for initially identifying all putative adverse outcomes through a broad search of the literature. The agency should then develop a process that uses guided expert judgment to identify the specific adverse outcomes to be investigated, each of which would then be subjected to systematic review of human, animal, and in vitro or mechanistic data.

- EPA should include protocols for all systematic reviews conducted for a specific IRIS assessment as appendices to the assessment.

Evidence Identification:
- The current process can be enhanced with more explicit documentation of methods. Protocols for IRIS assessments should include a section on evidence identification that is written in collaboration with information specialists trained in systematic reviews and that includes a search strategy for each systematic-review question being addressed in the assessment. Specifically, the protocols should provide a line-by-line description of the search strategy, the date of the search, and publication dates searched and explicitly state the inclusion and exclusion criteria for studies.

Evidence Evaluation:
- To advance the development of tools for assessing risk of bias in different types of studies (human, animal, and mechanistic) used in IRIS assessments, EPA should explicitly identify factors that can lead to bias in animal studies—such as control for litter effects, dosing, and methods for exposure assessment—so that these factors are consistently evaluated for experimental studies. Likewise, EPA should consider a tool for assessing risk of bias in in vitro studies.
• When considering any method for evaluating individual studies, EPA should select a method that is transparent, reproducible, and scientifically defensible. Whenever possible, there should be empirical evidence that the methodologic characteristics that are being assessed in the IRIS protocol have systematic effects on the direction or magnitude of the outcome. The methodologic characteristics that are known to be associated with a risk of bias should be included in the assessment tool. Additional quality assessment items relevant to a particular systematic review question could also be included in the EPA assessment tool.

• Although additional methodologic work might be needed to establish empirically supported criteria for animal or mechanistic studies, an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by EPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream.

• To maintain transparency, EPA should publish its risk-of-bias assessments as part of its IRIS assessments. It could add tables that describe the assessment of each risk-of-bias criterion for each study and provide a summary of the extent of the risk of bias in the descriptions of each study in the evidence tables.

• The risk-of-bias assessment of individual studies should be carried forward and incorporated into the evaluation of evidence among data streams.

Evidence Integration:
• EPA should continue to improve its evidence-integration process incrementally and enhance the transparency of its process. It should either maintain its current guided expert judgment process but make its application more transparent or adopt a structured (or GRADE-like) process for evaluating evidence and rating recommendations along the lines that NTP has taken. If EPA does move to a structured evidence-integration process, it should combine resources with NTP to leverage the intellectual resources and scientific experience in both organizations. The committee does not offer a preference but suggests that EPA consider which approach best fits its plans for the IRIS process.

• EPA should expand its ability to perform quantitative modeling of evidence integration; in particular, it should develop the capacity to do Bayesian modeling of chemical hazards. That technique could be helpful in modeling assumptions about the relevance of a variety of animal models to each other and to humans, in incorporating mechanistic knowledge to model the relevance of animal models to humans and the relevance of human data for similar but distinct chemicals, and in providing a general framework within which to update scientific knowledge rationally as new data become available. The committee emphasizes that the capacity for quantitative modeling should be developed in parallel with improvements to existing IRIS evidence-integration procedures and that IRIS assessments should not be delayed while this capacity is being developed.
Derivation of Toxicity Values:

- EPA should develop criteria for determining when evidence is sufficient to derive toxicity values. One approach would be to restrict formal dose-response assessments to when a standard descriptor characterizes the level of confidence as medium or high (as in the case of noncancer end points) or as "carcinogenic to humans" or "likely to be carcinogenic to humans" for carcinogenic compounds. Another approach, if EPA adopts probabilistic hazard classification, is to conduct formal dose-response assessments only when the posterior probability that a human hazard exists exceeds a predetermined threshold, such as 50% (more likely than not likely that the hazard exists).

- EPA should clearly present two dose-response estimates: a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived. The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value.