



July 15, 2014

The American Chemistry Council (ACC) is providing the comments below in response to a July 14, 2014 request from the Scientific Advisory Board Chemical Assessment Advisory Committee (CAAC) for the review of the Draft IRIS Ammonia Assessment. The text below is extracted from our 2012 ACC/ARASP comments on the draft IRIS handbook, which have already been submitted to the docket.¹

The current preamble does not provide a clear description of specific search strategies, exclusion and inclusion criteria, and weight of evidence approaches as the National Research Council (NRC) recommended. Instead, it provides an abbreviated view of EPA policies, guidance documents and standard practices, but fails to include the detail necessary to provide useful information on how the Agency reviews or weighs the scientific information for inclusion in the particular toxicological review. In providing this abbreviated view, critical information has been omitted and the preamble may lead readers to incorrectly interpret EPA guidance. In addition, we do not believe that it is appropriate to use the preamble as a means to communicate new criteria, guidance and approaches, that have not been properly peer reviewed, to the public. The adoption of new approaches should be done through an open and robust process that involves peer review and stakeholder participation before being implemented in an assessment. Specific examples are provided below.

A. PREAMBLE TO IRIS TOXICOLOGICAL REVIEWS

EPA discusses the preamble in Appendix B of Part 1 of the EPA Submission.² On August 6, 2012, ACC submitted comments to EPA on the draft ammonia assessment where we provided detailed comments on the draft preamble.³ EPA has noted that the new preamble was developed by the Agency in response to a recommendation from the NRC. However, in its review of EPA's draft formaldehyde assessment, NRC stated:

¹ The comments are available at:

[http://yosemite.epa.gov/sab/sabproduct.nsf/C4DE7217B460203285257CE800744E1E/\\$File/Attachment+1+ACC+ARASP+Comments+on+the+IRIS+Program+Jan+30+2013+Submissi+++pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/C4DE7217B460203285257CE800744E1E/$File/Attachment+1+ACC+ARASP+Comments+on+the+IRIS+Program+Jan+30+2013+Submissi+++pdf).

² The EPA submission to the NRC is available at: <http://www.epa.gov/iris/iris-nrc.htm>.

³ Comment submitted by Center for Advancing Risk Assessment Science and Policy (ARASP), <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2012-0399-0017>

Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria articulated and a better description of the outcomes of the searches and clear descriptions of the weight-of-evidence approaches used for the various non-cancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.

The current preamble does not sufficiently address the NRC's recommendation as it does not provide a clear description of specific search strategies, exclusion and inclusion criteria, and weight of evidence approaches. Specifically, as noted in our August 2012 comments on the preamble, as currently written, the preamble offers an abbreviated view of EPA policies, guidance documents and standard practices but fails to include the detail necessary to provide useful information on how the Agency reviews or weighs the scientific information for inclusion in the particular toxicological review. Unfortunately, in providing this abbreviated view, critical information has been omitted and the preamble may unduly lead readers to incorrectly interpret EPA guidance.

In addition to the general comments noted above we also provide some specific recommendations for improvements to the preamble. While EPA states that changes to the Preamble are fully implemented, further improvements are necessary.

- Section 2, Process for developing and peer-reviewing IRIS assessments: In this section the EPA has provided an overview of the May 2009 revised process for developing IRIS assessments.⁴ In step 4 of the development process, EPA estimates at least 3 ½ months for external peer review and comment, but does not specify specific time frames for public input prior to the draft assessment being released or denote a time frame for delivery of public comments to the peer review panel prior to the peer review meeting. Currently, when the draft toxicological reviews are released by the Agency they are near final – decisions about the main conclusions are presented as a *fait accompli*, stifling valuable input. Involving the public and other stakeholders earlier in the process will enable a more meaningful dialogue that can contribute to the development of the draft toxicological review. This engagement with stakeholders should include the identification of useful MOA information, applicable data evaluation frameworks to synthesize the scientific information being reviewed, relevant studies and data, as well as other relevant topics.
- Section 3, Identifying and selecting pertinent studies: This section provides a summary of the basic search strategy the Agency utilizes to gather scientific information for inclusion in the toxicological review and offers the key considerations used to select pertinent epidemiological and experimental studies. However, there are several areas where this section could be greatly improved.

⁴ U.S. EPA (2009). EPA's Integrated Risk Information System: Assessment development process. Available at: <http://epa.gov/iris/process.htm>.

- Section 3.2 provides some key considerations for selecting epidemiological studies and specifically states that “Cohort studies...provide the strongest epidemiological evidence, as they collect information about individual exposure.” However, not all cohort studies collect information based on individual exposure level; one example of this is cohort air pollution studies that are based on group level exposure (e.g., ambient monitoring). This section should provide clear guidance as to what type of information would generally be given more or less weight in the data evaluation framework.
- Sections 3.2 and 3.3 of the preamble purport to provide the key design considerations for selecting pertinent epidemiological and/or experimental studies from the results of the literature search and note exposure route and duration as key considerations. However, these sections do not provide the criteria used by the Agency for selecting studies. These sections should include all the considerations EPA utilizes in selecting a study for inclusion in the toxicological review and which of the criteria are deemed most necessary. Furthermore, EPA does not provide information that would allow the public to replicate EPA’s literature selection process for the chemical being assessed as recommended by NRC.
- Section 4, Evaluating the quality of individual studies: This section provides basic information on how the assessment evaluates various design and methodological aspects of the data that could increase or decrease the weight given to a study in the overall evaluations. Some examples listed in this section include: documentation of study design, exposure classification, disease classification and sample size. However, it is not clear which elements EPA deems most valuable for a study to possess for use in its data evaluation. The 2011 NRC report explicitly called on EPA to adopt standard data evaluation procedures/protocols for each of the major types of studies that typically need to be reviewed in conducting an IRIS assessment. To date, EPA has provided only very general considerations for study evaluations, and this falls short of what was recommended by the NRC. EPA can improve this section by:
 - Adopting clear and consistent guidance for evaluating studies. ARASP’s recent review of the existing methods currently used by environmental health agencies globally to establish study reliability and data quality for *in vivo* and *in vitro* studies shows that there are best practices the IRIS Program can immediately implement for these types of studies.⁵
 - Providing the specific elements or characteristics that would increase or decrease a study’s weight (e.g., does a low sample size decrease the weight of a study in the overall evaluation of the available scientific information). This section should include a list of the design or methodological aspects that increase weight and a list of the aspects that decrease weight.

⁵ Available at: <http://arasp.americanchemistry.com/Data-Quality-Evaluation>.

- Expanding the discussion on the use of historical controls. The draft assessment should clearly note that EPA's Cancer Guidelines⁶ discussion on the use of historical controls clearly states: "However, caution should be used in interpreting results."
- Section 5, Evaluating the overall evidence of each effect: This section discusses how the Agency evaluates the scientific evidence as a whole to determine the extent to which any observed association may be causally linked to the chemical of interest. EPA notes that positive, negative and null results are given weight according to the study quality and provides some aspects to consider in making that association to causality (i.e., strength of association, temporal relations, and biological plausibility). However, the section does not indicate how EPA assigns weight to studies or whether, for instance, studies of similar quality are given equal weight regardless of whether the study's results are positive, negative or null. EPA's weighting scheme should be discussed in more detail and clear criteria should be provided for increasing and decreasing weight. Information should be included in this section on how positive, negative and null studies are evaluated and weighted (i.e., are they given equal weight). The preamble also does not clearly identify which weight of evidence approach(es) EPA supports or utilizes. EPA should provide a listing of data evaluation practices that are used in the toxicological review. Additional examples where the section could be improved are provided below:
 - Section 5.1 begins to discuss the criteria for causality, but then moves away from causality to focus on determining whether or not an "association" exists. IRIS assessments should retain a focus on whether evidence of causality exists.
 - Section 5.2 provides some standard descriptors that may be used. EPA implies that suggestive epidemiologic information will be "consistent with causation" and the Agency does not seem to envision a scenario where there is suggestive epidemiologic information but a causal relation does not exist. The provided descriptors should capture all the realistic scenarios.
 - EPA's standard for suggestive evidence is typified when bias and confounding cannot be ruled out. However, such weak epidemiological evidence may not be consistent with causation. As currently formulated, EPA's criteria does not adequately capture such scenario and is needs to be modified.
 - Section 5.4, discusses evaluating MOA data and adverse outcome pathways. However the section does not discuss the concept of "significant biological support." This is an important concept in EPA's Cancer Guidelines. For instance, at page 3-23, the Cancer Guidelines state: "Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework." Different modeling approaches can be used even when there is a lack of MOA information.

⁶ U.S EPA (2005a). Guidelines for carcinogen risk assessment (EPA/630/P-03/001F). Available at: <http://www.epa.gov/cancerguidelines/>.

- Section 5.4 states: “Key data include the ability of the agent or a metabolite to react with or bind to DNA, positive results in multiple test systems, or similar properties and structure-activity relationships to mutagenic carcinogens (U.S. EPA, 2005a).” This statement, which implies that negative data would not be equally considered if it was of equal quality, does not appear to be included in EPA’s Cancer Guidelines. EPA should not use the preamble to establish new guidance. This sentence should be removed from the preamble.
- Section 5.5 seems to focus only on characterizing the overall weight of evidence for cancer and provides no guidance for non-cancer evaluations. In discussing the cancer evaluation, EPA notes that a narrative is provided that includes a standard hazard descriptor. EPA then provides the descriptors but provides no guidance for the narrative. This oversight should be corrected as the Cancer Guidelines correctly note that the complete narrative “preserves the complexity that is an essential part of the hazard characterization.” Guidance on preparing this narrative should be provided.
- Section 5.5 also provides an example of standard descriptors used for evaluating criteria pollutants. It is unclear what purpose this serves in the preamble. If EPA is suggesting that this approach will be adopted for use in the assessment, this should be clearly stated. Before implementation of a new approach, EPA must seek appropriate peer review and public comment.
- Section 6, Selecting studies for derivation of toxicity values: In this section EPA should be clear about existing guidance for when a toxicity value would not be derived. In particular, the Cancer Guidelines state:

When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates. Dose-response assessments are generally not done when there is inadequate evidence, although calculating a bounding estimate from an epidemiologic or experimental study that does not show positive results can indicate the study's level of sensitivity and capacity to detect risk levels of concern.
- Section 7, Deriving toxicity values: This section discusses how EPA derives toxicity values and conducts extrapolation to low doses. However, some oversights and inconsistencies should be addressed:
 - In Section 7.3, when discussing extrapolation and selection of a response level, EPA should note that the Benchmark Dose Technical Guidance⁷ suggests that an extra risk

⁷ EPA’s Benchmark Dose Technical Guidance (Risk Assessment Forum) June 2012. Available at: http://www.epa.gov/osa/raf/publications/benchmark_dose_guidance.pdf

of 10% is recommended as a standard reporting level for quantal data, for the purpose of making comparisons across chemicals or endpoints. For determination of a point of departure, a lower (or sometimes higher) response is often used based on statistical and biological considerations; nevertheless, for reporting purposes, it is recommended that the benchmark dose (BMD) corresponding to 10% extra risk always be presented.

- Section 7.4 incorrectly states that “linear extrapolation is also used if there is an absence of sufficient information on modes of action.” As noted previously, EPA’s Cancer Guidelines indicate that if there is “significant biological support”, and not a known mode of action, a non-linear extrapolation can be presented. Similarly, in describing when non-linear extrapolation is used, EPA again suggests that the MOA must be ascertained. This is not consistent with the Cancer Guidelines (see page 3-23). In addition, the Cancer Guidelines state that “Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach.”
- The approach described in Section 7.4 inappropriately interjects risk management into an IRIS assessment, under the veil of “scientific analysis.” EPA essentially asserts the default as “truth” and then requires that “sufficient” data be developed to refute the default. “Sufficient data” is never defined, and seems to be an ever moving target. This undermines research focused on applying modern techniques to improve the scientific evaluation of specific hypothesis as part of determining relevant modes of action. Instead of trying to ask and answer the question of “how much data and knowledge is enough to overrule a default?” what is needed is a framework that uses all of the relevant and reliable data and knowledge of hypothesized modes of action, in an open, objective and transparent manner, including, if warranted, valuation of the hypothesized MOA underlying the default.
- Section 7.6 does not adequately characterize what an oral reference dose (RfD) or an inhalation reference concentration (RfC) are because the text does not clearly state that RfD and RfC values are estimates, with uncertainty spanning perhaps an order of magnitude. EPA should correct its description in the preamble.
- Section 7.6 provides some discussion regarding uncertainty factors (UFs) however it is unclear what the Agency’s policy is on the application of UFs. In this section, EPA appears to create new policy by stating that the UF for human variation is reduced only if the point of departure is derived specifically for susceptible individuals. EPA should provide clear criteria for the application of UFs and discuss how the Agency considers UFs in totality to ensure that any compounding conservatism in the derivation of a toxicity value does not lead to an unrealistic final value.