Consolidated Comments from IRIS Interagency Reviewers on the Format and Preamble in the Science Consultation Draft Ammonia Assessment

June 2012

In 2011, the National Research Council (NRC) recommended[1] that EPA make changes in the development and presentation of Integrated Risk Information System (IRIS) assessments. The implementation of the NRC recommendations is following a phased approach that is consistent with their report. Along with streamlining assessments and increasing the use of tables, figures, and appendices, EPA has also changed the format of assessments and added a preamble. Prior to releasing the External Review Draft IRIS Toxicological Review of Ammonia, EPA circulated a previous version of the draft IRIS assessment preamble and assessment format to other Federal health agency scientists for their review and comment. The previous version was circulated as a part of Interagency Science Consultation[2] for an assessment other than ammonia, but the comments are applicable to the preamble and format in the draft IRIS Toxicological Review of Ammonia.

This document contains the comments provided by Federal health scientists outside of EPA on the previous draft version of the IRIS assessment preamble and format. Comments were received from the Council on Environmental Quality, Department of Defense, and the National Toxicology Program. These comments are being made publicly available to ensure transparency in the IRIS assessment development process.

[1] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

[2] Interagency Science Consultation is step 3 of the IRIS assessment development process. For more information, see http://www.epa.gov/IRIS/process.htm.

Interagency Comments

Council on Environmental Quality:

"The IRIS Program is to be commended on the new format for the toxicological reviews. The document is more accessible, easier to read, and there is greater transparency in the presentation of key assumptions. The effective use of figures and tables are also notable."

"In the preamble, we suggest adding some additional information (i.e., internet addresses) to the second paragraph in order to facilitate the reader's ability to locate assessments for the chemicals that are not covered by the IRIS program. We also suggest that you replace "White House offices" with Executive Office of the President offices."

"Finally, we recommend that the IRIS program consider modifying the new IRIS assessment format to include a section focused on the critical (or co-critical) study. For example, we think that some of the information about the critical study that presented in Appendix A could be moved into the main document and expanded upon."

Department of Defense:

Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 2/9/2012	
*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.			
Section	**Comment**	**Suggested Action, Revision and References (if necessary)**	***Category**
Preamble 2	EPA 2009 is not included in the list of references.	Add the reference to the list in Section 3.	E
Preamble, 3.3	Although this section explains the preferred types of exposures, the section does not contain definitions or examples. These definitions in the IRIS glossary are subject to change without notice. DoD would like to see contemporaneous definitions of "acute", "subchronic" and "chronic" exposures for both commonly used laboratory animals and people; these could be presented in a table.	Please supply definitions and examples of acute, subchronic, and chronic exposures for people and for all of the species that are used in the quantitative analysis of these chemicals.	S

Preamble, 4.2	In evaluating the quality of an epidemiological study, EPA does not include the need to demonstrate a reasonable dose-response relationship. As dose-response relationships are fundamental to all, high quality toxicological studies, this requirement, and whether the data must show a positive trend, a statistically significant increase, a biologically significant change, and/or other criteria should be presented in this section.	EPA should discuss its criteria with regard to dose-response observations for epidemiological studies. DoD notes in particular an over-reliance on statistics rather than biologically informative information, as well as an absence of a discussion about dose-response criteria.	S/M
Preamble, 4.3	In the third paragraph, EPA should state that it will clearly identify that its interpretation of the data differ from the scientists who conducted the study, as well as discussing why its conclusions differ. DoD would prefer if EPA would also commit to trying to contact at least one of the authors to determine their reaction to EPA's interpretation, and to allow those authors to comment on EPA's interpretation of the data, as they may have additional information about the study that was not published.	Disagreeing with the conclusions of the scientists who designed and conducted an experiment should only be done when there are clear and undisputed reasons. We suggest that EPA consider discussing its intended reinterpretation of the data with the authors before relying on a different interpretation for estimating toxicity of a chemical.	S
Preamble 5.2	DoD disagrees with EPA's statement that "causality is not at issue in controlled experiments". Unless a well designed experiment has been replicated exactly (often not the case for the critical experiment on which EPA bases its RfDs, RfC, and cancer potency values) statistically significant results can be false positives. At p = 0.05, there is a 1 in 20 probability of a false positive, even in a well controlled experiment.	EPA should delete this clause or provide at least one independent reference that would support its assertion.	S/M
Preamble 5.3	EPA's use of the term "genetic toxicity" is not defined and is neither clear nor transparent, especially in a section on mode of action (MOA). EPA's 2005 cancer guidelines and guidance do not use this term, but rather refer to a "mutagenic mode of action". Frequently, genetic toxicity includes effects that are not considered mutations, the term used in the rest of the document. DoD has previously mentioned EPA's tendency to use the terms "genotoxic" and "mutagenic" loosely, and as these terms have significant implications within EPA's guidelines and guidance, we would like to see more precision in their use.	We highly recommend that EPA define "genetic toxicity" and "mutagenicity" (or variants of those words), as they have significant implications within EPA's guidelines and guidance. The IRIS glossary does not include a reference for "genetic toxi8city" or "genotoxic"; and it does not always agree with definitions in other parts of EPA's web sites and can be changed without notice or review.	S/M
Preamble 5.4	The text does not mention a critical clause of the 2005 cancer guidelines: That the WOE for a chemical's MOA can vary by route of exposure or by level of exposure, etc. This section would be interpreted by many individuals as asserting that only one WOE is possible	EPA should include important options within this WOE section to clearly and accurately represent what is in its guidelines. The text should explicitly state that there can be more that one	S

	per chemical per endpoint.	WOE for carcinogenicity, e.g., a chemical's MOA can vary by route of exposure or by level of exposure, etc.	
Preamble, 7.3	EPA states that the choice of point of departure (POD) is based on statistical and biological factors and cites the draft BMD guidance (U.S. EPA 2000b) and EPA's 2005 guidelines for carcinogen risk assessment. The text goes on to state that for dichotomous responses, a 10% response will be used for "minimally adverse effects" and "5% or lower for more severe effects." Neither of the cited references have statements that agree with EPA's assertion. Both documents indicate that the benchmark response (BMR) that determines the POD should be near the low end of the range of data and that a 10% BMR should also be estimated for facilitating comparisons across chemicals. These concepts are also applied to the suggested methods for calculating the POD from continuous data. We know of no such severity-related guidance regarding the POD for nonlinear extrapolations in either of these documents. The definition of "minimally adverse" or "more severe" is a key aspect of the POD, but there is no available guidance as to how different effects should be categorized. Furthermore, the BMD guidance is listed in the references as U.S. EPA 2000a, rather than 2000b.	This language should be removed from the current Preamble and instead included in the BMD guidance document; such recommendations can be proposed by EPA and formally evaluated by the scientific and regulatory community. EPA should also correct the citations of EPA2000a vs. 2000b.	S/M
Preamble 7.3 and 7.4	These sections, that cover standard procedures used, contain several statements that are not consistent with EPA's 2005 cancer guidelines. If IRIS is proposing that these statements are standard practice within its toxicological review, it should both state that these are deviations and should provide a rationale for its deviation from guidelines. We believe that the cancer guidelines are applicable to the entire agency. 1. None of the cited EPA guidelines or guidance suggests use of a "standard value" for a point of departure for extrapolation, much less "(10% response for animal data, 1% for epidemiologic data, depending on the observed response rates)." These values are recommended as frequently used based on historical observations of results and the power of the standard studies. They are also recommended to be estimated and reported for the purposes	This section should be carefully reviewed to ensure consistency with EPA guidance and the references cited. 1. Please delete any reference to a standard response level or value for a POD for extrapolation. EPA's draft BMD and cancer guidelines refer to use of standard values for the purposes of comparisons among chemicals, and in that case the best estimate, not the lower confidence value, is recommended for use. 2. The use of the lower bound should be qualified, as it is in	S/M

	of comparing potencies across chemicals. The phrase that is in EPA's guidance is "near the low end of the observable range is used" which will differ by experimental design. 2. The statement that "For dichotomous responses, the point of departure is the 95% lower bound on the dose associated with a small increase of a biologically significant effect." requires addition of the qualifier "generally" or "usually" to be consistent with the cited sources. In particular, the BMD draft indicates that the maximum likelihood estimate should be used for some purposes. 3. EPA's guidelines discuss use of a biologically based model to extrapolate to lower doses. They do not advocate "Below the range where confidence bounds on the predictions are reasonably precise, extrapolation may continue using a linear model." 4. EPA's 2005 cancer guidelines differentiate low dose extrapolation procedures for MOAs that are linear at low doses, MOAs that are nonlinear (including nonlinear, no threshold) at low doses, and chemicals for which the MOA cannot be determined. They do not provide for a linear extrapolation "the dose response curve is expected to have **a linear component** below the point of departure. [emphasis added]" . As many highly nonlinear function have a "linear component" or can be fit to curves that have a linear component, this statement directly contradicts both the text and the intent of EPA's cancer guidelines. (DoD notes that the concept of a linear component is discussed with regard to chemicals with multiple MOAs, but does not make that a condition that requires a linear extrapolation.) 5. EPA's assertion that "Agents or their metabolites for which human exposures or body burdens are near doses associated with key events leading to an effect." is not included in the cited guidelines. IRIS has often asserted that IRIS documents do not consider exposure levels. If this is accurate, such a consideration is not relevant to this document. If IRIS documents do consider exposure levels, this	the cited references. 3. According to EPA's cancer guidelines, use of a biologically based model obviates extrapolation; linear or nonlinear. The statement should either be deleted or clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 4. The concept of a "linear component" or "other activity" as a criterion for determining whether the extrapolation is linear or nonlinear should be deleted as inconsistent with EPA's guidance. Otherwise, the text should clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 5. The suggestion that exposure levels are a criteria for type of extrapolation should either be deleted or EPA clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 6. IRIS documents should define the terms "genetic toxicity" and "mutagenicity", how they differ (if IRIS scientists believe they do), and how these definitions relate to EPA's mutagenic mode of action.	

	introduction should discuss those aspects of EPA's cancer guidelines that do refer to exposure, e.g., different WOEs for different levels of exposure. 6. The statement that "the agent does not demonstrate mutagenic or other activity consistent with linearity at lower doses." is not part of the criteria in EPA's cancer guidelines for using a non-linear extrapolation. The guidelines state that chemicals with a mutagenic MOA, not just mutagenic activity, are expected to have a linear extrapolation. This statement asserts a much lower criterion for imposing a linear extrapolation. Nor do the guidelines reference "other activity consistent with linearity" as a measure. The guideline only discusses such concepts within the context of the MOA, not individual key events of the MOA.		
Preamble 7.5	Statement #3 is incorrect. The cited EPA guidance document recommends use of the age-dependent adjustment factors ONLY for chemicals that have been demonstrated to have a mutagenic MOA that do not have chemical-specific data on early-life exposure, not "suspected carcinogens" as stated here.	EPA should correct this misstatement of policy.	S/M
Preamble 7.6	EPA states that "if the point of departure is based on toxicokinetic modeling, dosimetry modeling or allometric scaling", UFA = 10^0.5 is applied to account for "the remaining uncertainty involving toxicodynamic differences." The U.S. EPA (2011b) guidance states (p 21) that "processes pertinent to the consideration of this UF are recognized to include both toxicokinetics and toxicodynamics." While IRIS has instituted a "common practice" of asserting such a division after PBPK modeling, it should either provide a written citation for this practice, and indicate whether it has been externally peer reviewed, or explicitly state that this is an IRIS-developed policy that has or has not been externally peer reviewed. If such a guidance document is prior to 2011, it should also provide a rationale for not following the more recent guidance.	EPA should revise the text to accurately reflect U.S. EPA (2011b) guidance.	S

National Toxicology Program:

"This IRIS draft was prepared using a new format that has substantially decreased the unnecessary repetitions. The preamble section is extremely helpful for new readers and even the regulars. However, the formatting changes have also resulted into limited information on the studies that are critical and supportive of the guidance values derived. Therefore it is difficult to fully ascertain the scientific strengths or weaknesses from the summaries of the data presented. Also, the order of the sections in the document does not flow logically. Hopefully, these minor formatting issues would be sorted out with time."