EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Drafts of the IRIS Toxicological Review of Ammonia

May 2012

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Steps 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for drafts of the IRIS *Toxicological Review of Ammonia*.

Two versions of the draft ammonia assessment (dated October 2011 and February 2012) were sent to interagency reviewers for comments. The February 2012 draft was revised to be more streamlined and included a draft preamble, consistent with implementing 2011 recommendations on IRIS assessments from the National Research Council[1]. Comments on these draft ammonia assessments were received from the Agency for Toxic Substances and Disease Registry (ATSDR) and the Council on Environmental Quality (CEQ). In addition, comments on the format and draft preamble were received from some agencies in their review of another draft assessment that used the same formatting and preamble text. Although these interagency comments were submitted for an assessment other than ammonia, the comments are applicable to the preamble and format in the interagency review draft IRIS Toxicological Review of Ammonia. These comments on the changes to format and the draft preamble were received from CEQ, Department of Defense (DOD) and the National Toxicology Program and are provided with the Interagency Science Consultation draft ammonia assessment. All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website www.epa.gov/IRIS.

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

Interagency Science Consultation Comments—Selected Major Comments and Responses:

Topic #1: Suggested addition of a developmental toxicity study – ATSDR suggested that the following paper be added to the Toxicological Review:

> Miñana, MD; Marcaida, G; Grisolia, S; et al. (1995) Prenatal exposure of rats to ammonia impairs NMDA receptor function and affords delayed protection against ammonia toxicity and glutamate neurotoxicity. J Neuropathol Exp Neurol 54(5):644-650.
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> **EPA Response**: EPA considered the study by Miñana et al. (1995) in developing the Toxicological Review of Ammonia. Miñana et al. (1995) investigated the effects of ammonium acetate on the function of certain receptors in brain nerve cells in rats exposed during gestation and lactation. As discussed in the Preface of the Toxicological Review, this assessment addressed the toxicity of gaseous ammonia (NH_3) and ammonia dissolved in water (ammonium hydroxide, NH_4OH); because there is evidence that ammonium salts differ from ammonia in their toxicity, the toxicological literature on ammonium salts was outside the scope of this assessment. Because Miñana et al. (1995) studied the effects of ammonium acetate—an ammonium salt, this study was not included in the draft Toxicological Review.

Topic #2: Consistency of elements of the Preamble with EPA guidelines – The Toxicological Review of Ammonia includes a new preamble that describes the application of existing EPA guidance and the methods and criteria used in developing IRIS assessments. The new preamble includes information 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. DOD offered a series of comments asserting that elements of the draft preamble were inconsistent with EPA risk assessment guidelines. Specific comments are summarized and addressed below.

- DOD commented that none of the cited EPA guidelines suggests use of a "standard value" for a point of departure for extrapolation, much less 10% response for animal data and 1% for epidemiologic data (depending on the observed response rates) as stated in the preamble.

  EPA Response: For dichotomous data, EPA guidance recommends specific response levels for use across IRIS assessments to derive the point of departure (POD) for extrapolation. For example, EPA's draft 2000 *Benchmark Dose Technical Guidance Document* states "the actual 'benchmark dose' used as a POD may correspond to

response levels below (or sometimes above) 10%, although for convenience standard levels of 1%, 5%, or 10% have typically been used" (p. 19). Further, this guidance document states that "[a]n excess risk of 10% has generally been the default BMR for quantal data" (p. 19) and that "epidemiology studies often have greater sensitivities and a BMR of 1% has typically been used for quantal human data" (p. 20). Similarly, EPA's 2005 *Guidelines for Carcinogen Risk Assessment* ("Cancer Guidelines") state that "[c]onventional cancer bioassays, with approximately 50 animals per group, generally can support modeling down to an increased incidence of 1–10%; epidemiologic studies, with larger sample sizes, below 1%" (p. 3-17).

In recognition of the fact that selection of the response level used to derive a POD takes into consideration factors such as study design, sensitivity of the study, and nature or adversity of the effect, the text in Section 7.3 of the preamble was revised to better reflect those considerations. Although consistent values for response levels are generally used across IRIS assessments consistent with Agency guidance, EPA agreed that these response levels did not need to be characterized as "standard values" and revised the text of this section of the preamble accordingly.

- DOD observed that EPA's Cancer Guidelines differentiate low-dose extrapolation procedures for modes of action (MOAs) that are linear at low dose, MOAs that are nonlinear at low doses, and chemicals for which the MOA cannot be determined. DOD commented that the guidelines do not provide for a linear extrapolation where "the dose response curve is expected to have a linear component below the point of departure" as stated in the preamble.

  EPA Response: The text highlighted by DOD from Section 7.4 of the draft preamble is a quote from the Cancer Guidelines (p. 3-21). Since the language in the preamble is an accurate reflection of EPA guidelines, no changes to this part of the preamble were made.

- DOD stated that the following language from Section 7.4 of the draft preamble is not included in the cited guidelines: "Agents or their metabolites for which human exposures or body burdens are near doses associated with key events leading to an effect."

  EPA Response: The text in Section 7.4 of the preamble is not an exact quote from EPA's Cancer Guidelines (p. 3-21), but closely follows the wording in the Cancer Guidelines (provided below):

> *Linear extrapolation* should be used when there are MOA data to indicate that the dose-response curve is expected to have a linear component below the POD. Agents that are generally considered to be linear in this region include:…
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> - agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process…

The small changes to the text taken from the Cancer Guidelines were made only to more effectively and concisely capture the key points from the guidelines.

- DOD commented that, contrary to the text of the preamble, 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 nonlinear extrapolation. Rather, DOD commented, the guidelines state that chemicals with a mutagenic MOA, not just mutagenic activity, are expected to have a linear extrapolation.

  EPA Response: The text highlighted by DOD from Section 7.4 of the draft preamble is a quote from the Cancer Guidelines (p. 3-22). Since the language in the preamble is an accurate reflection of EPA guidelines, no changes to this part of the preamble were made.

Topic #3: Other suggested revisions to the Preamble – Other comments were offered by Federal agencies and CEQ to improve the clarity and completeness of the draft preamble.

EPA Response: EPA appreciated the input provided during the Interagency Science Consultation step and incorporated a number of the suggested revisions to the preamble.