NCEA Proposed Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of Ammonia

August 2013

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the draft Toxicological Review of Ammonia that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). An existing assessment for ammonia, which includes an inhalation reference concentration (RfC), was posted on IRIS in 1991.

IRIS is a human health assessment program that evaluates scientific information on effects that may result from exposure to specific chemical substances in the environment. Through IRIS, EPA provides high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information for chemical substances that can be used to support the first two steps (hazard identification and dose-response assessment) of the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for chronic health effects (including cancer and effects other than cancer). Government and others combine IRIS toxicity values with exposure information to characterize public health risks of chemical substances; this information is then used to support risk management decisions designed to protect public health.

The external review draft Toxicological Review of Ammonia is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans and experimental animals exposed to ammonia. Only data using ammonia or ammonium hydroxide were considered in this review; data developed using ammonium salts were not considered because of concerns that the effects of the counter ion might confound the study outcomes. This draft IRIS assessment includes:

- a *Preamble* to describe the methods used to develop IRIS assessments;
- an *Executive Summary* to concisely summarize the major conclusions of the assessment;
- a *Literature Search Strategy/ Study Selection and Evaluation* section to describe the process for identifying and evaluating the evidence for consideration in developing the assessment;
- a *Hazard Identification* chapter to systematically synthesize and integrate the available evidence of organ/system-specific hazards; and
- a *Dose-Response Analysis* chapter to describe the selection of studies for consideration in calculating toxicity values and to describe the analysis and methodology in deriving and selecting toxicity values.

Additionally, appendices for chemical and physical properties, toxicity of ammonium salts, toxicokinetic information, summaries of toxicity studies, and other supporting materials are provided as *Supplemental Information* (see Appendices A to G) to the draft Toxicological Review. The draft assessment was developed according to guidelines and technical reports published by EPA (see Preamble), and contains a qualitative characterization of the hazards for ammonia, including a cancer descriptor of the chemical's human carcinogenic potential and a noncancer toxicity value for chronic inhalation exposure (RfC). A chronic oral reference dose (RfD) was not derived and a quantitative cancer assessment for ammonia was not conducted due to inadequate

data.

Charge Questions

In April 2011, the National Research Council (NRC) released its *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC included comments and recommendations for improving the development of IRIS assessments. The IRIS Program's implementation of the NRC recommendations is following a phased approach. Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments that had been near the end of the development process and close to final posting. The IRIS Program is now in Phase 2 of implementation, which addresses all of the short-term NRC recommendations. The Program is implementing all of these recommendations but recognizes that achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and external peer review committees. This phased approach is consistent with the NRC's *Roadmap for Revision* as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others."

Below is a set of charge questions that address scientific issues in the draft IRIS Toxicological Review of Ammonia. The charge questions also seek feedback on whether the document is clear and concise, a central concern expressed in the NRC report. Please provide detailed explanations for responses to the charge questions. EPA will also consider the Science Advisory Board review panel's comments on other major scientific issues specific to the hazard identification and dose-response assessment of ammonia. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

General Charge Questions:

1. NRC (2011) indicated that the introductory section of IRIS assessments needed to be expanded to describe more fully the methods of the assessment. NRC stated that they were "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 [toxicity values]." Please comment on whether the new *Preamble* provides a clear and concise description of the guidance and methods that EPA uses in developing IRIS assessments.

2. NRC (2011) provided comments on ways to improve the presentation of steps used to generate IRIS assessments and indicated key outcomes at each step, including systematic review of evidence, hazard identification, and dose-response assessment. Please comment on the new IRIS document structure and whether it will increase the ability for the assessments to be more clear, concise, and easy to follow.

3. NRC (2011) states that "all critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated" and that "strengthened, more integrative, and more transparent discussions of weight of evidence are needed." NRC also indicated that the changes

suggested would involve a multiyear process. Please comment on EPA's success thus far in implementing these recommendations.

Chemical-Specific Charge Questions:

A. Executive Summary

1. The major conclusions of the assessment pertaining to the hazard identification and dose-response analysis have been summarized in the *Executive Summary*. Please comment on whether the conclusions have been clearly and sufficiently described for purposes of condensing the Toxicological Review information into a concise summary.

B. Literature Search Strategy/Study Selection and Evaluation

1. The process for identifying and selecting pertinent studies for consideration in developing the assessment is detailed in the *Literature Search Strategy/Study Selection and Evaluation* section. Please comment on whether the literature search approach, screening, evaluation, and selection of studies for inclusion in the assessment are clearly described and supported. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of ammonia.

C. Hazard Identification

Synthesis of Evidence

1. A synthesis of the evidence for ammonia toxicity is provided in Chapter 1, *Hazard Identification*. Please comment on whether the available data have been clearly and appropriately synthesized for each toxicological effect. Please comment on whether the weight of evidence for hazard identification has been clearly described and scientifically supported.

Summary and Evaluation

2. Does EPA's hazard assessment of noncancer human health effects of ammonia clearly integrate the available scientific evidence (i.e., human, experimental animal, and mechanistic evidence) to support the conclusion that ammonia poses a potential hazard to the respiratory system?

3. Does EPA's hazard assessment of the carcinogenicity of ammonia clearly integrate the available scientific evidence to support the conclusion that under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "inadequate information to assess the carcinogenic potential" of ammonia?

D. Oral Reference Dose (RfD)

An RfD was not derived for ammonia based on insufficient data. Human data involving oral exposure to ammonia are limited to case reports involving intentional or accidental ingestion and repeat exposure animal studies are limited in scope and designed to investigate mechanisms by which ammonia can induce effects on the gastric mucosa of rats.

1. Please comment on whether the rationale for not deriving an RfD is scientifically supported and clearly described. Please comment on whether data are available to support the derivation of

an RfD for ammonia. If so, please identify these data.

2. As described in the Preface, data on ammonium salts were not considered in the identification of effects or the derivation of an RfD for ammonia and ammonium hydroxide because of concerns about the potential impact of the counter ion on toxicity outcomes. Please comment on whether the rationale for this decision is scientifically supported and clearly described.

E. Inhalation Reference Concentration (RfC)

An RfC was derived for ammonia based on effects on the respiratory system, which was identified as the primary and most sensitive target of inhaled ammonia. An occupational epidemiology study by Holness et al. (1989), with the support of three other occupational epidemiology studies by Rahman et al. (2007), Ali et al. (2001), and Ballal et al. (1998), was selected as the principal study for RfC derivation. Decreased lung function and respiratory symptoms were selected as the critical effect.

1. Please comment on whether the evaluation and selection of studies and effects for the derivation of the RfC is scientifically supported and clearly described. Please identify and provide the rationale for any other studies or effects that should be considered.

2. The NOAEL/LOAEL approach was used to identify the point of departure (POD) for derivation of the RfC. Please comment on whether this approach is scientifically supported and clearly described.

3. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on the recommendations described in Section 4.4.5 of *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

F. Quantitative Cancer Assessment

1. Quantitative cancer estimates were not derived for ammonia because of inadequate information. Please comment on whether the rationale for not deriving quantitative cancer estimates for ammonia is scientifically supported and clearly described. Please comment on whether data are available to support a quantitative cancer assessment. If so, please identify these data.

G. Endogenous Production of Ammonia

1. Ammonia is produced endogenously and has been detected in the expired air of healthy volunteers. Please comment on whether the discussion of endogenous ammonia in Section 2.2.4 of the Toxicological Review is scientifically supported and clearly described.