

**Summary Minutes of the  
U.S. Environmental Protection Agency  
Science Advisory Board  
Chemical Assessment Advisory Committee Augmented for the  
Review of the Draft IRIS Ammonia Assessment (CAAC-Ammonia Panel)  
Public Face-to-face Meeting  
July 14-16, 2014**

**Meeting Participants**

**CAAC-Ammonia Panel Members:**

Dr. Michael Dourson, CHAIR  
Dr. Daniel Acosta  
Dr. Henry Anderson  
Dr. Scott Bartell  
Dr. Arthur Cooper  
Dr. David Eastmond  
Dr. William Michael Foster  
Dr. Russ Hauser  
Dr. Abby A. Li  
Dr. Jacob McDonald  
Dr. Maria Morandi  
Dr. Victoria Persky  
Dr. Kenneth Ramos  
Dr. Alan Stern  
Dr. I. David Weiner

**SAB Staff:** Dr. Sue Shallal, Designated Federal Officer

**Other Attendees:** see Appendix A

**Location:** Crowne Plaza Washington National Airport, 1480 Crystal Drive, Arlington, VA, 22202

**Purpose:** To receive briefings on the EPA's enhancements to the IRIS Program, including the process for developing IRIS assessments. The panel also will be briefed on the development of the EPA's *IRIS Toxicological Review of Ammonia (August 2013)* and begin their deliberations to develop responses to the EPA charge questions.

**Meeting Materials:**

The materials listed below may be found on the meeting webpage at:

<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/3C012EC41FBC420085257C98006459B9?OpenDocument>

- Agenda
- Federal Register Notice
- Panel Roster
- Agency Charge

- Agency Briefing Material
  - Advances in Systematic Review by Samantha Jones
  - IRIS Enhancements by Vince Cogliano.
  - Overview of IRIS Ammonia Assessment by Susan Reith.
  - Upcoming Activities by Gina Perovich.
- Presentation by Registered Public Speaker
  - Presentation by Dr. Jill Ryer-Powder on behalf of The Fertilizer Institute.
  - Statement submitted by Nancy Beck of the American Chemistry Council.
- Public comment submitted to the SAB Staff Office
  - Comments submitted by Mr. Kevin Bromberg of the U. S. Small Business Administration.
  - Comments submitted by Mr. Wade Foster of The Fertilizer Institute.
- Committee Members' Comments
  - Preliminary Comments Submitted by Dr. Arthur Cooper.
- Committee-Developed or Provided Background Material
  - Citation provided by Dr. Arthur Cooper. References and background materials. References submitted by Dr. David Eastmond.

**Meeting Summary:**

The discussion followed the general plan as presented in the meeting agenda.

**Monday July14, 2014**

**Opening Remarks**

Dr. Shallal, the Designated Federal Officer (DFO), convened the meeting and called the roll. All CAAC-Ammonia panel members were present except Drs. Hauser and McDonald. Dr. Pleus withdrew from participation in the review due to other commitments. Dr. Shallal welcomed panel members and members of the public to the second meeting of the SAB CAAC- Ammonia Panel. The first was a teleconference held on June 2, 2014. She explained that the SAB CAAC-Ammonia Panel operates under the auspices of the Federal Advisory Committee Act (FACA).

The SAB is an independent, expert federal advisory committee chartered under the authority of the Federal Advisory Committee Act (FACA). The SAB is empowered by law, the Environmental Research, Development, and Demonstration Authorization Act (ERDDAA), to provide advice to the EPA Administrator on scientific and technical issues that support the EPA's decisions. The DFO noted that the Federal Register notice announcing the meeting had provided the public with an opportunity to provide written and oral comment. The DFO stated that the SAB consists entirely of special government employees (SGEs) appointed by EPA to their positions. As SGEs, chartered SAB members are subject to all applicable ethics laws and implementing regulations. EPA has determined that advisors participating in this meeting have no financial conflicts of interest or appearance of a loss of impartiality under ethic regulations specified in 5 CFR 2635 relating to the topic of this meeting.

The DFO also reminded all participants that the meeting materials were available on the SAB website. Then, Mr. Christopher Zarba, the Director of the SAB Staff Office, welcomed and thanked panel members for their willingness to serve on this panel. Finally, Dr. Shallal turned the meeting over to Dr. Dourson, Chair of the CAAC-Ammonia Review Panel.

Dr. Dourson reviewed the agenda and asked panel members to briefly introduce themselves. He told the panel and audience members that the morning session would be devoted to a briefing on the agency's progress in implementing the NRC recommendations for improving IRIS assessments. He then invited the EPA representatives to begin their presentations.

### **EPA presentations on the IRIS Program**

Dr. Kenneth Olden, Director of EPA's National Center for Environmental Assessment (NCEA), provided some opening remarks. He stressed the commitment of the IRIS program to be more transparent and engage in meaningful dialogue with stakeholders at multiple intervals during the development of IRIS assessments. Dr. Cogliano, Acting Director of the EPA's IRIS Program, provided an overview of the IRIS program and the efforts to implement the recommendations of the NRC (presentation posted on the SAB website).

Panel members asked clarifying questions about the time it takes to complete an IRIS review, the use of NIH criteria in the systematic review of studies, the use of only peer-reviewed studies and ensuring the incorporation of recommendations by the CAAC panel. Dr. Cogliano responded that IRIS reviews generally take 2 ½ to 3 ½ years to complete. He noted that NIH relies on medical interventional studies and EPA often relies on observational studies; some of the criteria are therefore not applicable. He explained that EPA uses peer-reviewed published studies because they have been vetted and are publicly available. He also assured panel members that their advice is valued and will be incorporated in the revisions to the draft assessment.

The next speaker was Dr. Samantha Jones, Associate Director for Science for EPA's IRIS Program, who presented information on EPA's approach for systematic review of the literature (presentation posted on the SAB website). She stated that the IRIS program is implementing systematic review methods. She also noted that these methods will evolve and will be strengthened by experience and following advice from the NRC and SAB, and getting feedback from stakeholders. Panel members then discussed different approaches for evaluating studies, including the Klemish approach. Dr. Jones responded that a variety of approaches are possible and the IRIS program is still considering which one(s) to adopt.

Dr. Gina Perovich, Acting Deputy Director of the IRIS Program, talked about the upcoming activities of the IRIS Program (presentation posted on the SAB website). She stated that the enhancements to the IRIS program were being implemented in a step-wise manner. She explained how the structure of the IRIS assessments had changed and the enhancements that are anticipated for future assessments. IRIS assessments will include more public input early in the scoping and problem formulation phase, throughout the information gathering phase and during the peer review period.

After returning from the lunch break, the afternoon session began with Dr. Dourson's review of the portion of the agenda devoted to the review of the agency's draft IRIS assessment of Ammonia. He then invited Ms. Susan Reith of the IRIS program to give an overview of the draft IRIS Ammonia assessment.

### **EPA Overview of the draft IRIS Ammonia Assessment**

Ms. Reith presented the key findings in the draft IRIS Ammonia assessment (presentation posted on the SAB website). She stated that the reference concentration (RfC) of 0.3 mg/m<sup>3</sup> was based

on decreased lung function and respiratory symptoms as seen in occupational epidemiology studies. She commented that the reference dose (RfD) was not derived because data were not sufficient to allow for such a derivation. For the cancer finding, she noted that there was inadequate information to assess ammonia's carcinogenic potential. She also provided information to address some of the questions that were raised by panel members and the public during the June 2, 2014 teleconference. She explained that the RfC is not based on the Acute Exposure Guideline Levels (AEGLs) because they are developed with an assumption of an "once-in-a-lifetime" exposure scenario. She added that AEGLs do not take into account either potential for repeated spikes in exposure or repeated injury leading to the potential for a cumulative increase in effect.

### **Public comments**

Dr. Dourson then asked the registered public speakers to present their comments (see Appendix B). Nancy Beck, presenting on behalf of the American Chemistry Council (ACC), said that the Preamble needed revision (presentation posted on the SAB website). She commented that the principles of systematic review had not been followed for the EPA's draft ammonia assessment. She also suggested that an independent monitor should review final assessments to ascertain if recommendations had been incorporated.

Dr. Dourson asked if EPA representatives had any clarifying comments regarding the Preamble. Dr. Cogliano of EPA noted that the Preamble was intended to be general and not specific to each assessment. The Preamble will undergo further refinement based on comments received from the NAS, SAB and public commenters.

Dr. Jill Powder, speaking on behalf of The Fertilizer Institute (TFI) (presentation posted on the SAB website), stated that TFI is advocating the use of a point of departure (POD) of 25 ppm. She commented that this level is scientifically based and health-protective. She further contended that it is supported by the principal study (Holness et al.) and consistent with the IRIS process.

After Dr. Powder's presentations, panel members discussed the appropriateness of using the AEGL for deriving the RfC. A panel member noted that the 25 ppm level was based on occupational exposure studies with a duration of 8 hours and needs to be adjusted to 24 hours. Also, members added that the Preamble for AEGL documents says that these levels should not be used as limits of exposure for the general population.

### **Discussion of the Charge Questions**

Dr. Dourson explained that the panel will be discussing the Charge Questions in a slightly different sequence than how they appear in the agency's request (see Agency Charge on Meeting Material Webpage). He stated that the panel will begin their deliberations with question B1 and continue to question G1 then return to question A1. The *General Charge Questions* on the new IRIS process and structure of the IRIS assessments will be discussed after completing the chemical-specific questions.

### **B. Literature Search Strategy/Study Selection and Evaluation**

#### **Question # B1**

Panel members stated that, in Figure LS-1 on page xxxviii of the draft ammonia assessment, the exclusion criteria were not clearly presented. Evaluation of co-exposures (e.g., smoking) and risk

of bias concerns were not addressed adequately in the assessment. More explanation about how studies were evaluated and why some were excluded and others included needs to be added.

The panel commented that the rationale for excluding ammonium salts needs further clarification. In order to explain why an oral RfD was not derived, a better explanation of why ammonium salts were not included in the assessment is needed.

Briefly, the panel agreed that the

- Table on page xxxviii should be clarified
- Exclusion rationale for ammonium salts should be clarified
- Focus of the assessment should be clarified early
- Co-exposure information should be made available
- Expand the discussion of smoking and polycyclic musks as confounding factors in the studies

### C. Hazard Identification

#### *Synthesis of Evidence*

##### Question # C1

The panel commented that the tables provide good information but should be expanded and reformatted. A more systematic method for presenting the study results would be helpful. Information such as number of animals or subjects and p values is needed. The panel agreed that the Holness et al. study was the appropriate one to use.

The issue of tolerance was discussed and thought to be important in considering the effects of ammonia on lung function. Hyperammonemia causes harmful effects on brain; those with liver disease may be more susceptible.

Information on mechanism of action (MOA) should be highlighted more, especially gastric mucosal thinning. More description of the studies is needed in the tables in the main document to help the reader understand more about the quality of the studies.

In summary, there should be some balance between brevity and too much detail provided in the main document. The tables need to be expanded to include more information about the studies. Inhalation is the right focus when discussing endpoints of concern. The discussion of ammonium salts and rationale for non-inclusion should be expanded.

The meeting recessed at approximately 5:30 p.m. until the following morning.

### **Tuesday July 15, 2014**

Dr. Shallal opened the meeting and stated that it was a continuation of the previous day's discussion of the EPA's draft assessment of ammonia. She made an announcement concerning Dr. Acosta's change of status on the panel. Dr. Acosta had been a member of the standing SAB Chemical Assessment Advisory Committee but had recently taken a position with the U.S. Food

and Drug Administration. As a federal employee, he was no longer eligible to serve on a SAB standing committees; however, Dr. Acosta would continue as a panel member.

Dr. Dourson then invited panel members to add any comments about the questions that were discussed on the previous day before continuing with the next question, # C2.

Members noted that with regard to question #B1, some references were missing and a more systematic approach to evaluating the studies was needed. Others added that it was not apparent whether the missing studies were not found or were eliminated because they were rejected after being evaluated. The panel also noted that the EPA should be encouraged to implement more of the NAS recommendations (e.g., contacting the authors to get additional information). Nonetheless, panel members agreed that significant progress had been made. Additionally, panel members commented that mechanistic data should be presented clearly along with the criteria for evaluating and formulating the weight of evidence (WOE).

### C. Hazard Identification

#### *Summary and Evaluation*

##### Question # C2

The panel agreed that the critical effect of exposure to ammonia is on the respiratory system effecting lung function. The Holness et al. study did show a decrease in lung function (i.e., decreased Forced Expiratory Volume, FEV). Additional information about the mode of action should be added to clarify why the RfD was not derived.

The charge question was revised by the panel during its June teleconference to include **systemic toxicity through other routes**; after additional discussion, the panel agreed to disregard this addition and to respond to the question as it had been originally written.

##### Question # C3

The panel commented that ammonia had been described as a promoter of carcinogenicity. The panel agreed that there was not enough information to assess ammonia's cancer potential. Furthermore, the panel noted that there was no evidence of cancer via a systemic route of exposure in studies of hyperammonemia.

### D. Oral Reference Dose (RfD)

#### Question # D1

The panel noted there are short term studies that show thinning of the gastric mucosa. The panel also commented there is not enough information to conclude that the gastric mucosal thinning would progress. The panel suggested that an expansion of the discussion was needed to explain why the studies using ammonium salts were not considered in the assessment. The criteria for when studies are considered weak should be better defined.

#### Question # D2

The panel noted it is important to understand that there is no such thing as pure ammonia. Ammonia is always in a state of equilibrium between ammonium and ammonia (i.e.,  $\text{NH}_3$  gas  $\leftrightarrow$   $\text{NH}_3/\text{NH}_4^+$   $\leftrightarrow$   $\text{NH}_4^+$ ). A description of the chemistry of ammonia/ammonium would be helpful. The panel also commented that the preparation of the administered ammonia in the

various studies may be important and may impact the effects. A better discussion to explain the findings of studies that used ammonium sulfate versus ammonium chloride versus ammonium acetate would be helpful to show the diversity of effects.

After returning from a lunch break, the panel continued its discussion of the study using ammonium chloride. They noted that there were no effects on gastric mucosa even after 2 years of exposure. The panel concluded that a more thorough evaluation and better description of the findings associated with the exposure to different ammonium salts should be included in the assessment.

#### E. Inhalation Reference Concentration (RfC)

##### Question # E1

The panel noted that there was no mention of the exclusion of chamber studies in the main document. The Holness study was preferred because it provided the best measurements of exposure and also had the highest no observed adverse effect level (NOAEL). The panel suggested that the description of the effects on the forced expiratory volume (FEV) within the assessment should be expanded. A discussion of the 4 studies ensued (Ballal, Ali, Rahman, and Holness). The panel commented that the totality of evidence is more important to understanding the adverse outcome than any one observation. A better, expanded discussion of the rationale for the selection of the critical effect is needed; the additional studies can be used to support the weight of evidence.

##### Question # E2

The panel stated that the right study (i.e., Holness et al.) was selected and an apparent dose/response curve can be seen when using all the studies. Using the combination of studies to select a NOAEL is logical and reasonable. The quality of the exposure data in the Rahman study may not have allowed the use of that study; contacting the author is an option for getting the raw data. Benchmark dose modeling may be possible if more data is available by contacting the author.

The panel concluded that using the threshold limit values (TLVs) is not appropriate. There are still adverse effects that occur at these levels; they are not NOAELs.

The Ballal study corroborates EPA's choice of a point of departure; the discussion should be expanded to include this information. The healthy worker effect should also be considered.

The panel agreed with the use of the Holness study but suggested that EPA try to characterize a midpoint. The panel noted that using an arithmetic mean of the highest dose group may be a better measure due to the short duration of exposure. The panel suggested that EPA should try to contact the author (i.e., Holness) to get individual level data so that dose-response modeling may be attempted.

##### Question # E3

The panel agreed that the use of uncertainty factors followed EPA guidance. The panel noted that eye and mucosal irritation are acute responses. Irritation has both toxicokinetic and toxicodynamics components therefore a 10X UF is correct. To move to greater or lesser than 10 X factor, more data would be required - an expanded clearer explanation is needed

## F. Quantitative Cancer Assessment

### Question #F1

The panel agreed with EPA's conclusion that there was inadequate data to support a quantitative cancer assessment

The meeting recessed at approximately 5:30 p.m. until the following morning.

## **Wednesday June 16, 2014**

## G. Endogenous Production of Ammonia

### Question # G1

Panel members discussed several items related to endogenous production of ammonia in the appendices that require revision. The panel noted that hyperammonemia causes an increase in glutamate in the brain, ammonia is synthesized in the liver, and released from skeletal muscle during exercise. Ammonia is excreted from the nose and mouth at very low levels.

A discussion of how exhaled ammonia would impact the NOAEL ensued. Exhaled ammonia will not alter ambient levels. The amount of ammonia that is exhaled should not impact safe levels. For example, CO<sub>2</sub> or mercury levels that are exhaled are not safe to inhale.

## A. Executive Summary

### Question #A1

The panel recommended that the discussion within the assessment be improved and the changes reflected in the Executive Summary. A description of the chemistry of ammonia should be added and the scope of the document better defined and justified. The RfD section should be strengthened with more discussion of the chronic studies. Sensitive populations/ life stages should be addressed for inhalation effects, such as those who are asthmatics or have COPD along with appropriate references. Studies of children are available that show the developing brain is more susceptible. More information about the tumor promoter potential of ammonia should be included. The production of endogenous ammonia should be summarized and the glutamate pathway added.

## General Charge Questions:

### General Question #1

In the Preamble, the short summaries of the various guidance documents is very good. The discussion of the derivation of toxicity values /selection of studies is both helpful and useful. Six criteria are listed but they are not the ones used in this assessment. It should be explained that this is not a comprehensive list. The weight of evidence (WOE) section should be expanded to cover non-cancer endpoints. The ammonia assessment should not be delayed due to these recommendations.

### General Question #2

The organization is logical and headings are appropriate. The document was easier to read – following the rationale was simpler. Panel members were pleased with the use of tables; however, the tables should be revised (e.g., Trimethylbenzenes Assessment tables are more useful). The inclusion of negative results in the tables, NOAEL/LOAEL, low and high range of each study and distinguishing between good versus supplemental information would be helpful. Finally, the panel suggested that the description of the key studies should be included in the main document.

### General Question #3

The panel commented that the assessment was easy to read. The panel noted that the study selection/evaluation criteria were explained well in the preamble; however, criteria for selecting animal studies/data and epidemiology studies/data was lacking in the main text. Keeping in mind that there are more improvements to come, the study evaluation criteria should be explicitly described. For this document, studies were evaluated in a sound manner but not in a standardized way. Panel members stated that they did not want to recommend a specific methodology for evaluating the studies but rather they would provide examples of such approaches. Panel members suggested that an additional column be added to the tables included in the assessment explaining why a study was excluded – e.g., utility for risk assessment, for deriving a NOAEL or LOAEL, was used as supplemental information.

### General Question #4

The panel stated that EPA was responsive to the public comments. The panel commented that TLVs are not protective of the general population and should not be used in the assessment. The panel suggested that transparency is most important and not necessarily satisfying a specific stakeholder.

### Clarifying Comments

Gina Perovich of EPA thanked the panel for its work. She noted that approaches for systematic review are being discussed and input from a variety of stakeholder and advisory groups is being sought.

An announcement was made to see if members of the public wanted to make any additional comments to the panel – no one wanted to comment.

### Summary of Major Recommendations

For the Assessment, the major recommendations are:

- EPA attempts are good thus far
- Ammonia versus ammonium needs further discussion as they relate to the derivation of the reference dose (RfD)
- The discussion of whether or not to consider studies on ammonium salts should be expanded
- Appropriate study is Holness et al. – contact author to get raw data
- For a quantitative cancer assessment, there is insufficient data
- Default uncertainty factor of 10 is appropriate for development of the RfC

- Further expand the discussion of endogenous ammonia

For the General Charge Questions, the major recommendations are:

- Preamble is a good idea
- Use of tables is helpful – should be refined with additional descriptors
- Work to standardize study selection process
- Study selection criteria for exclusion needed
- A more systematic approach is underway for animal studies
- Expand search for studies using ammonium salts
- Regarding the NAS report – EPA is moving in the right direction

### **Next Steps**

Panel members were asked to provide the following:

By Monday July 28 – individual comments are due

By August 11 – lead discussant write-up

By August 18 – final response to charge question is due

The meeting was adjourned at approximately 4:00 p.m.

Respectfully Submitted,

/s/

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Suhair Shallal, Ph.D.  
Designated Federal Officer

Certified as Accurate:

/s/

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Michael Dourson, Ph.D.  
Chair, SAB CAAC-Ammonia Review Panel

**NOTE AND DISCLAIMER:** The minutes of this public meeting reflect diverse ideas and suggestions offered by panel members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

## APPENDIX A

### List of Attendees and those requesting teleconference access- July 14-16, 2014 Meeting

July 14, 2014

<b>Name</b>	<b>Affiliation</b>
Angela Nugent	EPA
Tom Brennan	EPA
Audrey Galizia	EPA
Susan Rieth	EPA
Kevin Bromberg	SBA-Advocacy
Vincent Cogliano	EPA
Nancy Beck	ACC
Samantha Jones	EPA
Pat Rizzuto	Bloomberg BNA
Jill Powder	TFI
Louis D'Amico	EPA
Maria Hegstad	Inside EPA
Ted Berner	EPA
Gina Perovich	EPA
Glenda Cooper	EPA
Wade Foster	TFI
Nina Wilson	Gowan
Chris Zarba	EPA
Alan Sasso	EPA

July 15, 2014

<b>Name</b>	<b>Affiliation</b>
Audrey Galizia	EPA
Chris Zarba	EPA
Susan Rieth	EPA
Kevin Bromberg	SBA-Advocacy
Vincent Cogliano	EPA
Samantha Jones	EPA
Jill Powder	TFI
Maria Hegstad	Inside EPA
Ted Berner	EPA
Glenda Cooper	EPA
Wade Foster	TFI
James Kim	OMB
Nina Wilson	Gowan

July 16, 2014

<b>Name</b>	<b>Affiliation</b>
Tom Brennan	EPA
Audrey Galizia	EPA
Susan Rieth	EPA
Vincent Cogliano	EPA
Samantha Jones	EPA
Pat Rizzuto	Bloomberg BNA
Jill Powder	TFI
Maria Hegstad	Inside EPA
Ted Berner	EPA
Ravi Subramani	EPA
Nina Wilson	Gowan

Requested teleconference number

<b>Name</b>	<b>Affiliation</b>
Belinda Hawkins	EPA
Christine Ross	EPA
Jamie Schenk	SBA-Advocacy
Haylie Choi	EPA
Robert Fensterheim	EPA

## **APPENDIX B**

**U.S. ENVIRONMENTAL PROTECTION AGENCY  
SCIENCE ADVISORY BOARD  
Chemical Assessment Advisory Committee Augmented for the  
Review of EPA's Draft Ammonia Assessment (CAAC-Ammonia Panel)  
List of Registered Speakers  
July 14-16, 2014**

1. Dr. Jill Powder on behalf of The Fertilizer Institute
2. Dr. Nancy Beck of the American Chemistry Council