US Environmental Protection Agency
EPA Science Advisory Board
Summary Meeting Minutes of a Public Teleconference Meeting
2:00 pm - 5:00 pm (Eastern Time)
November 27, 2006

Committee: U.S. Environmental Protection Agency's Chartered Science Advisory Board (SAB). (See Roster - Attachment A.)

Date and Time: November 27, 2006, 2:00 pm - 5:00 pm (Eastern Time) (see Federal Register Notice – Attachment B)

Location: Participation by Telephone Only

Purpose: To review a draft SAB Panel draft report, *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic* (See Meeting Agenda - Attachment C.)

Attendees: Chartered SAB Members:
Dr. James Bus
Dr. Deborah Cory-Slechta
Dr. Baruch Fischhoff
Dr. James Galloway
Dr. Rogene Henderson
Dr. James Johnson
Dr. Meryl Karol
Dr. George Lambert
Dr. Jill Lipoti
Dr. Michael J. McFarland
Dr. M. Granger Morgan, Chair
Dr. Rebecca Parkin
Dr. Stephen Roberts
Dr. Joan Rose
Dr. Kathleen Segerson
Dr. Deborah Swackhamer
Dr. Thomas L. Theis
Dr. Valerie Thomas
Dr. Robert Twiss
Dr. Lauren Zeise

Chair of the SAB Arsenic Review Panel: Dr. Genevieve Matanoski

Liaison with EPA's Children's Health Advisory Panel: Dr. Melanie Marty

EPA SAB Staff Office: Dr. Angela Nugent, Designated Federal Officer for the teleconference; Mr. Thomas Miller, Designated Federal Officer for the SAB Arsenic Review Panel; and Dr. Vanessa Vu, Director

Members of the Public Presenting Oral Comment:
Dr. Barbara D. Beck, Gradient Corporation
Dr. Gary Kayajanian
Dr. Steven H. Lamm, Georgetown University
Dr. Lorenz Rhomberg, Gradient Corporation
Dr. Rosalind A. Schoof, Integral Consulting Inc.

Other Members of the public (see Attachment D)

Meeting Summary:

The meeting followed the issues and general timing as presented in the meeting Agenda, except where otherwise noted (see Meeting Agenda - Attachment C). Written comments were submitted to the SAB and five members of the public presented oral comments during the teleconference.

The DFO opened the meeting by noting that the proceedings conformed to the requirements of the Federal Advisory Committee Act and that the members of the chartered SAB had met the requirements of the Ethics in Government Act.

Dr. M. Granger Morgan introduced the quality review and acknowledged the work of the SAB Arsenic Review Panel and the Panel Chair, Dr. Genevieve Matanoski. Dr. Matonoski provided brief comments summarizing the panel's work on inorganic and organic arsenic in three principal areas: metabolism of arsenic, the mode of action, and the dose-response.

Dr. Morgan asked the public speakers to provide their brief oral comments. , Dr. Rosalind Schoof commented on the dose-response for inorganic arsenic. She requested several changes to the text and references in the draft report in sections 4.5.2 and 3.5.2 related to arsenical pesticides and asked for the draft document to expand its discussion of exposures at lower doses. She also requested corrections to several statements cited from her research.

Dr. Lawrence Rhomberg commented on three points. He asked that the draft cover letter and executive summary of the report be more consistent concerning the cancer-slope factor with points made in the body of the report regarding meta-analysis and sensitivity analysis. He asked for consideration of the "Taiwan Data" that showed a threshold below which there were no effects and for a discussion of the application of EPA's Cancer Guidelines discussion of non-linear extrapolation.

Dr. Stephen Lamm's comments related to his extensive written comments provided to the committee. He asked the SAB to consider the Southwest Taiwan data

that he had analyzed and his finding that inconsistencies and confounding factors in those data raise issues about carcinogenicity. He also asked the SAB to consider the 133-county study that examined response at low dosages.

Dr. Gary Kayajanian's comments expanded on his written comment provided to the committee. He asked the committee to consider epidemiological data he viewed as relevant to the human low-dose extrapolation discussions in sections B.3, C.2, and D.2 of the draft report. He requested the SAB to consider the data provided by Dr. Lamm on effects at low dosages and asked that the draft cover letter discuss the dose response for human data in low dose region as consistent with a negative and linear slope.

Dr. Barbara Beck asked the SAB to expand the thoughtful, comprehensive draft report to address studies not included in the EPA report and to provide a more complete discussion of EPA's cancer guidelines. She asked that Dr. Lamm's data be considered, as well as a meta-analysis of studies showing carcinogenicity at lower doses. She discussed the plausibility of a non-linear dose-response model, given significant biological support and emerging epidemiological data.

Dr. Matanoski responded briefly that the SAB Arsenic Review Panel had made a conscious decision that it would not reanalyze data considered by the Agency, other than data associated with the mode of action for DMA5. She noted that the Arsenic Review Panel had already considered much of the data provided by public commenters. Although the draft report does not specifically address the merits of these data, it advises EPA to address them.

Dr. Morgan then recognized the Lead Reviewers to give their specific comments about the report. Dr. Lauren Zeise summarized major points in her written comments provided to the chartered SAB. Among those points, she noted that animal data do not suggest a linear response for inorganic arsenic; that the report should consider the "power" of different studies in evaluating the extent to which inorganic arsenic supports non-linearity; that the report include additional discussion about the relationship between DMA and TMA formation in humans; that the panel clarify text on page 19 concerning TMA formation in rats; that the draft report consider additivity whenever discussing mechanisms of action, especially genotoxicity; that the report consider recent studies on transplacental carcinogenicity; that the report fully evaluate the range of adverse effects at different levels of exposure and different life stages; and that the panel consider her written comments regarding uncertainty factors associated with inorganic arsenic.

Dr. Deborah Cory-Slechta, the second Lead Reviewer, agreed that the report needed to take special note of arguments concerning the decreasing uncertainty factor for inorganic arsenic and reconsider the discussion of uncertainties associated with TMA on pages 19 and 22 to clarify its rationale for readers. She suggested that the report provide bounding numbers rather than general references to "low" or "high" values. She also suggested that the report could benefit from a consistent approach to formatting for highlighting conclusions related to major charge questions.

Dr. James Bus, the third Lead Reviewer, complimented the panel for a thoughtful draft report and for advising EPA to choose a different mode of action for DMA. He noted that the letter and executive summary of the report did not capture the thrust of text in the major report, which called for consideration of a non-linear risk assessment model for inorganic arsenic. He suggested that the letter, executive summary, and report would be more transparent if the language was more consistent. He noted that it would be helpful if the report more clearly identified the epidemiological literature that would be useful for EPA to review. He also suggested that, given the biological model discussed and the availability of epidemiology data, the report might advise the Agency to consider a low-dose, non-linear dose response for inorganic arsenic.

At the Chair's suggestion, Dr. Matanoski briefly responded to the lead reviewers' comments. She noted that the panel had not agreed that the dose-response was non-linear for inorganic arsenic. She observed that it would "make sense" to make more prominent in the response advice that the Agency should undertake analyses of other models, such as lung cancer.

Dr. Morgan suggested that, where the panel could easily do so, it would be valuable for the draft report to identify key research needs associated with the major areas of uncertainty. Dr. Matanoski responded that the panel was well-organized to address such a task.. Dr. Matanoski responded that the panel was well-organized to address such a task.

Dr. Morgan asked members of the chartered SAB and the liaison member from the Children's Health Protection Advisory Committee for any additional comments. Most members participating in the call referenced their written comments (see Attachment E). The points emphasized included: a) the need for discussion of sensitivity and uncertainty related to toxicity parameters; b) the need to address variability in individual sensitivity at low dosages and sensitive subpopulations; c) the need to communicate more clearly the carcinogenic model of DMAV and the significance of rat bladder tumors; d) the need to consider whether there is perhaps yet an additional mode of action not covered in the EPA analysis; e) the significance of genotoxicity; f) the difference between the terms "no-threshold" and "non-linear"; and g) a recently published epidemiological study on effects in children.

A member of the chartered SAB moved that the chartered SAB conditionally approve the report subsequent to a) revision of the report by the Chair of the Panel, Dr. Matanoski, working with the SAB Staff Office, to address issues raised during the chartered SAB members' teleconference discussion, and b) additional review by Drs. Bus, Cory-Slechta, and Zeise. The motion was seconded and passed without objection or abstentions.

<u>Decision and Action Item:</u>

The Chartered SAB approved the draft SAB Panel draft report, *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic* subject to: a) Dr.

Matanoski's working with the SAB Staff Office to address issues raised during the chartered SAB members' teleconference discussion and b) additional review by Drs. Bus, Cory-Slechta, and Zeise.

The teleconference was adjourned at 4:15 p.m.

Respectfully Submitted:	Certified as True:
/Signed/	***/Signed/***
Angela Nugent Designated Federal Official	M.Granger Morgan Chair Science Advisory Board

List of Attachments

Attachment A: Roster of the Chartered Science Advisory Board

Attachment B: Federal Register Notice

Attachment C: Meeting Agenda

Attachment D: Attendees from the Public Who Did Not Provide Oral Comment

Attachment E: Compilation of Comments from Members of the Chartered SAB and Liaison Members

Attachment A: Roster of the Chartered Science Advisory Board

CHAIR

Dr. M. Granger Morgan, Head and Professor, Department of Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA

SAB MEMBERS

Dr. Gregory Biddinger, Environmental Programs Coordinator, ExxonMobil Biomedical Sciences, Inc, Houston, TX

Dr. James Bus, Director of External Technology, Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, MI

Dr. Trudy Ann Cameron, Raymond F. Mikesell Professor of Environmental and Resource Economics, Department of Economics, University of Oregon, Eugene, OR

Dr. Deborah Cory-Slechta, Director, Environmental and Occupational Health Sciences Institute, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey and Rutgers University, Piscataway, NJ

Dr. Maureen L. Cropper, Professor, Department of Economics, University of Maryland, College Park, MD

Dr. Virginia Dale, Corporate Fellow, Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN

Dr. Kenneth Dickson, Professor, Institute of Applied Sciences, University of North Texas, Denton, TX

Dr. Baruch Fischhoff, Howard Heinz University Professor, Department of Social and Decision Sciences, Department of Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA

Dr. James Galloway, Professor, Department of Environmental Sciences, University of Virginia, Charlottesville, VA

Dr. Lawrence Goulder, Shuzo Nishihara Professor of Environmental and Resource Economics, Department of Economics, Stanford University, Stanford, CA

Dr. James K. Hammitt, Professor of Economics and Decision Sciences, Harvard Center for Risk Analysis, Harvard University, Boston, MA

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

Dr. James H. Johnson, Professor and Dean, College of Engineering, Architecture & Computer Sciences, Howard University, Washington, DC

Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

Dr. Meryl Karol, Professor Emerita, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

Dr. Catherine Kling, Professor, Department of Economics, Iowa State University, Ames, IA

Dr. George Lambert, Associate Professor of Pediatrics, Director, Center for Childhood Neurotoxicology, Robert Wood Johnson Medical School-UMDNJ, Belle Mead, NJ

Dr. Jill Lipoti, Director, Division of Environmental Safety and Health, New Jersey Department of Environmental Protection, Trenton, NJ

Dr. Michael J. McFarland, Associate Professor, Department of Civil and Environmental Engineering, Utah State University, Logan, UT

Dr. Judith L. Meyer, Distinguished Research Professor Emeritus, Institute of Ecology, University of Georgia, Athens, GA

Dr. Jana Milford, Associate Professor, Department of Mechanical Engineering, University of Colorado, Boulder, CO

Dr. Rebecca Parkin, Professor and Associate Dean, Environmental and Occupational Health, School of Public Health and Health Services, The George Washington University Medical Center, Washington, DC

Mr. David Rejeski, Director, Foresight and Governance Project , Woodrow Wilson International Center for Scholars, Washington, DC

Dr. Stephen M. Roberts, Professor, Department of Physiological Sciences, Director, Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL

Dr. Joan B. Rose, Professor and Homer Nowlin Chair for Water Research, Department of Fisheries and Wildlife, Michigan State University, East Lansing, MI

Dr. Jerald Schnoor, Allen S. Henry Chair Professor, Department of Civil and Environmental Engineering, Co-Director, Center for Global and Regional Environmental Research, University of Iowa, Iowa City, IA

Dr. Kathleen Segerson, Professor, Department of Economics, University of Connecticut, Storrs, CT

Dr. Kristin Shrader-Frechette, O'Neil Professor of Philosophy, Department of Biological Sciences and Philosophy Department, University of Notre Dame, Notre Dame, IN

Dr. Philip Singer, Professor, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC

Dr. Robert Stavins, Albert Pratt Professor of Business and Government, Environment and Natural Resources Program, John F. Kennedy School of Government, Harvard University, Cambridge, MA

Dr. Deborah Swackhamer, Interim Director and Professor, Institute on the Environment, University of Minnesota, Minneapolis, MN

Dr. Thomas L. Theis, Director, Institute for Environmental Science and Policy, University of Illinois at Chicago, Chicago, IL

Dr. Valerie Thomas, Anderson Interface Associate Professor, School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, GA

Dr. Barton H. (Buzz) Thompson, Jr., Robert E. Paradise Professor of Natural Resources Law, Stanford Law School, and Director, Woods Institute for the Environment, Stanford University, Stanford, CA

Dr. Robert Twiss, Professor and Emerita, University of California-Berkeley, Ross, CA

Dr. Terry F. Young, Consultant, Environmental Defense, Oakland, CA

Dr. Lauren Zeise, Chief, Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA

Attachment B: Federal Register Notice

EPA Science Advisory Board; Notification of a Public Teleconference of the Science Advisory Board

[Federal Register: October 24, 2006 (Volume 71, Number 205)]
[Notices]
[Page 62257-62258]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr24oc06-45]

ENVIRONMENTAL PROTECTION AGENCY
[FRL-8233-6]

EPA Science Advisory Board; Notification of a Public Teleconference of the Science Advisory Board

AGENCY: Environmental Protection Agency.
ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Science Advisory Board (SAB) Staff Office announces a public teleconference of the Chartered Board to review a draft SAB report, Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic.

DATES: The SAB will hold the public teleconference on November 27, 2006. The teleconference will begin at 2 p.m. and end at 5 p.m. (Eastern Time).

ADDRESSES: Telephone conference call only.

FOR FURTHER INFORMATION CONTACT: Any member of the public wishing to obtain general information concerning this public teleconference should contact Dr. Angela Nugent, Designated Federal Officer (DFO), EPA Science Advisory Board (1400F), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; via telephone/ voice mail: (202) 343-9981; fax: (202) 233-0643; or e-mail at: nugent.angela@epa.gov. General information concerning the EPA Science Advisory Board can be found on the EPA Web site at: http://www.epa.gov/sab.

SUPPLEMENTARY INFORMATION: Pursuant to the Federal Advisory Committee Act, Public Law 92-463, notice is hereby given that the EPA SAB will

hold a public teleconference to review a draft SAB report. The SAB was established by 42 U.S.C. 4365 to provide independent scientific and technical advice to the Administrator on the technical basis for Agency positions and regulations. The SAB is a Federal Advisory Committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The SAB will comply with the provisions of FACA and all appropriate SAB Staff Office procedural policies.

Background: The purpose of the public teleconference is to review the SAB Arsenic Review Panel's draft report, Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic. In reviewing draft reports from its panels, the SAB considers whether: (i) The original charge questions to the SAB review panel were adequately addressed in the draft report, (ii) the draft report is clear and logical; and (iii) the conclusions drawn, or recommendations made in the draft report, are supported by the body of the report.

The draft report to be reviewed at this public teleconference focuses on several issues about the mode of carcinogenic action of various arsenic species and the implications of these issues for EPA's assessment of the cancer hazard and risks of organic and inorganic arsenic. The panel reviewed a science issue paper prepared by EPA's Office of Pesticide Programs (with an attachment prepared by EPA's Office of Research and Development) and a revised hazard and dose response assessment/characterization for inclusion in EPA's Integrated Risk Information System (IRIS) prepared by EPA's Office of Water. Additional information about the SAB Arsenic Assessment Review Panel can be found on the web at:
http://www.epa.gov/sab/panels/arsenic_review_panel.htm.

Availability of Teleconference Materials: The draft agendas and other materials will be posted on the SAB Web site at:
http://www.epa.gov/sab/ prior to the teleconference.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral information for the SAB to consider during the public teleconference. Oral Statements: In general, individuals or groups requesting an oral presentation at a public SAB teleconference will be limited to three minutes per speaker, with no more than a total of one-half hour for all speakers. Interested parties should contact Dr. Angela Nugent, DFO, in writing (preferably via e-mail), by November 16, 2006, at the contact information noted above, to be placed on the public speaker list for this teleconference. Written Statements: Written statements should be received in the SAB Staff Office by November 16, 2006, so that the information may be made available to the SAB for their consideration prior to this teleconference. Written statements

should be supplied to the DFO in the following formats: One hard copy with original signature, and one electronic copy via e-mail (acceptable file format: Adobe Acrobat PDF, WordPerfect, MS Word, MS PowerPoint, or Rich Text files in IBM-PC/Windows 98/2000/XP format).

Accessibility: For information on access or services for individuals with disabilities, please contact Dr. Angela Nugent at (202) 343-9981 or nugent.angela@epa.gov. To request accommodation of a disability, please contact Dr. Nugent preferably at least ten days prior to the teleconference, to give EPA as much time as possible to process your request.

Dated: October 17, 2006.

Anthony F. Maciorowski,

Associate Director for Science, EPA Science Advisory Board Staff Office.

[FR Doc. E6-17803 Filed 10-23-06; 8:45 am]

BILLING CODE 6560-50-P

Attachment C: Meeting Agenda

US Environmental Protection Agency
Chartered Science Advisory Board (SAB) Public Teleconference

November 27, 2006; 2:00 p.m. – 5:00 p.m. Eastern Time

Meeting Location: Via Telephone Only

(Call-in information is available at (202) 343-9999)

2:00 p.m.	**Convene the Teleconference Meeting** DFO's Introductory Statement	Dr. Angela Nugent Designated Federal Officer (DFO) US EPA SAB Staff Office
	Introductory Remarks of the Chair	Dr. M. Granger Morgan Chair, EPA SAB
2:15 p.m.	**Introduction to the draft SAB Panel Report** ***Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic***	Dr. Genevieve Matanoski, Chair of the Panel
2:30 p.m.	**Public Comments**	See Attached List (3 minutes per speaker)
3:00 p.m.	**Chartered SAB Quality Review Discussion**	Lead Discussants: Dr. James Bus Dr. Deborah Cory-Slechta Dr. Lauren Zeise General Discussion by Members of the Chartered SAB Members of the Chartered SAB
4:00 p.m.	**Summary and Action items**	Dr. M. Granger Moran
5:00 p.m.	**Adjourn the Meeting** (Time Approximate)	Dr. Angela Nugent

List of Public Commenters

Speaker	Affiliation	On behalf of:
Dr. Barbara D. Beck	Gradient Corporation	Monomethyl Arsenic Acid Task Force
Dr. Gary Kayajanian		Self
Dr. Steven H. Lamm	Georgetown University	Monomethyl Arsenic Acid Task Force
Dr. Lorenz Rhomberg	Gradient Corporation	Wood Preservative Science Council
Dr. Rosalind A. Schoof	Integral Consulting Inc.	Self

Attachment D: Attendees from the Public Who Did Not Provide Oral Comment

Robert E. Adamski

Barbara D. Beck

Nancy Beck

Sue Dempsey

Rick Graham

Carl Herbrandson

Angus R. Kelly

Don Lore

Loren Lund

Brian A. Mayes

Darrell Osterhoudt

Amy L. Perbeck

Gloria B. Post

Barbara T. Walton

Luanne Williams

Attachment E: Compilation of Comments from Members of the Chartered SAB and Liaison Members

Compilation of Comments Received as of November 27, 2006 from Chartered SAB Members and Chartered SAB Liaison Members on draft SAB Report: *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic*

1. Dr. James Bus

The EPA SAB Advisory Review Panel has conducted a very thorough and thoughtful review of the EPA analysis of the assessment of the carcinogenic effects of organic and inorganic arsenic. The Panel has offered detailed and clear responses to the charge questions of the review, and in general, has offered conclusions and recommendations that are fully supported by the draft report.

When the Review Panel has offered opinion that differs from those of the EPA review documents, it has provided extensive text and associated documentation that will prove useful for consideration by agency scientists. A particularly good example of this is the Review Panel's extensive commentary on the Mode of Action (MOA) of DMA, in which they provide useful analysis supporting their advocacy of an alternative non-linear cytotoxicity based MOA compared to the linear, oxidative-stress toxicity MOA proposed by EPA. This reviewer concurs with the Review Panel's alternative MOA recommendation and its implications for selection of a non-linear risk assessment model.

The letter to the Administrator and associated recommendation in the review indicates the Panel concurs *for now* with the EPA's proposal to apply a linear risk assessment approach for iAs. However, the Panel's review provides extensive commentary in response to charge question B3 (pp. 29-37) suggesting that animal, associated in vitro evidence, and even human genotoxicity data are highly suggestive that iAs should be expected to have a threshold. Similarly, much of the Panel's analysis of the epidemiology data (see section 3.5.2; p. 48-50) illustrates its weaknesses in illuminating the shape of the dose response below 100 ppb iAs exposure. The Panel goes on to suggest useful directions for further characterization of the epidemiology that ultimately might define future refinements in selection of risk assessment models for cancer risk of iAs. However, both the letter to Administrator and the primary conclusions presented in the Executive Summary do not seem to reflect the Panel's overall tone regarding their implied concerns surrounding use of a linear risk evaluation assessment of iAs-induced human cancer. The Panel should consider if their analysis is sufficient to suggest that the Agency, for the sake of transparency to future risk management decisions, consider developing alternative non-linear approaches to the evaluation of iAs carcinogenicity, and further, pointing to key data that, if generated, would be sufficient to justify both the use and selection of such alternative approaches.

Specific comments:

Letter to the Adminstrator, p.2, ll. 22-27, ll. 37-38: The statements here do not seem to adequately capture the tone of the review regarding iAs cancer risk, i.e., that further research into the animal mode of iAs and exploration of human epidemiology at <100 ppb iAs may well steer the future risk assessment to non-linear alternatives.

Executive Summary:

p. 6, ll. 4-12: This summary does not seem to adequately reflect the strength of conclusions reached in the main body of the review on p. 36, ll. 37-38 and p.37, ll. 1-4 regarding the likelihood that iAs cancer may involve a threshold response.

Review Body:

p.30, Table 1: Should altered DNA methylation be listed?

p.34, l.27: The description of theWaalkes et.al study might benefit from an expanded description of the dose-response, if conducted, in this study, and its implications for selection of risk models.

p.37, ll. 1-4: The review is perhaps a bit inconsistent with respect to its recommendation to use a non-linear model for DMA based entirely on animal evidence (appropriate!) and essentially no epidemiology, but proposes retaining application of a linear model for iAs even though both animal MOA and human genotoxicity data suggest potential non-linear outcomes and epidemiology data if viewed as "lacking or problematic". However, I concur with the conclusion that resolution of this issue through future research is "extremely important", a conclusion intensity that perhaps could be amplified in the both the Letter and the Executive Summary conclusions and recommendations.

p.39, ll. 21-25: The Panel indicates the studies of Gur et.al. would be very valuable in evaluating DMA MOA, but must be published and/or peer reviewed in order to fulfill that promise. This important conclusion is missing from the Executive Summary.

p.43, ll. 27-36: This conclusion provides excellent future research direction.

p.45, l. 30: If the toxicity/carcinogenicity of DMA is indeed due to its reduction, and this process is "saturable" as suggested here, it does indeed indicate potential "non-linear" toxicity responses, but not necessarily threshold-based responses? Saturation of reduction would seem to limit the upper-end responses of the dose-response, i.e., causing a plateau due limitation in the amounts of toxic reduced DMA?

p.46, ll. 22-24: This wording seems a bit odd, and perhaps could more directly state that EPA's position on a linear oxidative stress MOA is likely not defensible and should not be used.

2. Dr. Deborah Cory-Slechta

General Comment:

The Panel is to be congratulated for a very thorough response to a complex and extensive set of questions. It is clear that the Panel gave quite careful consideration to all of the questions. Some general suggestions are addressed at making the document more readable.

1. The conclusions in many sections get lost in the presentation of the arguments presented. For some charge questions, the conclusions are presented first, followed by text. In other sections, they appear in the midst of the text, and in some cases, they appear at the end. It would be useful to have a more consistent approach. In addition, it would be useful to change the formatting of the document to highlight those conclusions of the panel that are the specific answer to the charge question.
2. The sections describing MOAs include little in the way (for the most part) of direct comparisons of dose levels, i.e., they don't generally compare the effects at which these various observations occur, but rather present descriptions, e.g., 'low' etc. This section would probably be more useful if such information were presented, recognizing the difficulties and lack of direct comparisons in some cases. But it would further strengthen the arguments for the answer arrived at by the Panel.
3. Page 29-37 It would be very helpful to readers to have this section written with some conclusions at the end of each paragraph or after related paragraphs. It currently reads as a presentation of a significant number of studies, but the basis for their presentation is not clear, and the points that are attempting to be made by this section are being lost. This section could either include sub-titles that specifically state those conclusions or some other mechanism of making clear the basis for the inclusion of this material.
4. p. 19. Lines 1-18. It seems somewhat strange that statements are made about the potential for less severe outcomes in humans base don the fact that there is no metabolism to trimethylarsine species given that there is no statements cited that it is the TMA species that are more toxic or cause the toxicity. In the absence of that information, it doesn't seem appropriate to make that assumption. The answer to this is actually presented on p. 22, lines 31-37; this information should either be moved up or included in the response on p. 19 as well.
5. p. 46, lines 16-18, not a sentence.
6. p. 49, line 22, delete space between 'relations' and hips'
7. P. 58-61. Response to charge question D5. The answer seems to be to carry out sensitivity analyses, which is listed as a non-bolded two word phrase on p. 60, line 12.

3. Dr. Baruch Fishchoff

No comments

4. Dr. James Galloway

I have read the report and I have no comments.

5. Dr. Rogene Henderson

Comments of Rogene Henderson, Nov.17, 2006

I have reviewed the letter and the executive summary of this report.

a) I found the report to be highly responsive to the charge questions. Each question was discussed and the SAB Panel provided a clear response.

b) The draft report was clear, logical and easy to read. It is well-organized around the charge questions.

c) I am still reviewing the body of the report. The parts I have read support the conclusions given in the letter and in the executive summary.

6. Dr. Jill Lipoti

I have reviewed the draft report, Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic. I have no comments. The charge questions were adequately addressed.

7. Dr. Meryl Karol

This is an excellent draft report that effectively addresses the charge questions. The report is logical and clear, and its conclusions are supported in the text of the report. The following points are suggested for clarification/grammatical considerations:

· Letter – correct grammar, p. 2, line 22 change is to are; and line 25, but they the data do fit with a linear model.
· p. 34 line 28, unclear what is meant by "the document".
· p. 34 line 29, should read neither iAsIII nor iAsV is a are complete ….
· p. 35, last sentence. Do the authors wish to imply that all As species contribute to the toxicity in tissues. I suggest the authors consider rewording line 19 as follows "from all diverse species present in that tissue.

8. Dr. Melanie Marty

1. Page 18, line 6-8. In describing the toxicokinetics of DMA^V, there is mention of the demethylation to inorganic arsenic in the gut. This should be quantified if possible by the Agency since it is taking the position that DMA has a nongenotoxic mode of action in part because the metabolism of DMA does not appear to lead to inorganic arsenic. Transformation to inorganic arsenic and subsequent absorption across the gut may then exposure cells directly to inorganic arsenic which is genotoxic and does not necessarily have a nonlinear MOA.

2. Page 26 lines 4-9. The advisory states very strongly that ROS-induced DNA damage by DMA^V is not important for carcinogenesis (stated as "the principal MOA for DMA^V is not mediated by ROS-induced DNA damage pathway"), and states the MOA is likely to be sustained cytotoxicity followed by genomic instability as a result of stress-related proliferation. This conclusion seems overstated. Genomic instability might in part be the result of ROS-mediated DNA damage. It is not clear to me that you can or should separate these phenomena so neatly, and the Panel could reword that sentence to indicate that ROS mediated DNA damage may play a role in DMA carcinogenicity but does not appear to be the principal MOA.

3. Section 3.3.3.Page 29- 32. I agree that the Panel should endorse a linear dose-response model for inorganic arsenic carcinogenicity. However, the discussion in this section downplays the role of genotoxicity, including oxidative DNA damage, from inorganic As in carcinogenicity. The text seems to want to disregard positive genotoxicity results because arsenic is a potent cytotoxin and thus "A genotoxic effect can only be a MOA if it occurs in living cells and if the genotoxic effect is consistent with effects seen in tumorigenesis studies and in human tumors." Not all cells with mutations induced by arsenite will die. Arsenic is clearly carcinogenic to humans, and there aren't good animal models of arsenic-induced carcinogenesis, so tumorigenesis studies are difficult. Hence, it is not clear what utility this argument has in the advisory.

   On page 33, the advisory states on line 33-34 that the role of ROS in low dose arsenic carcinogenesis is "probably via signaling changes rather than as a genotoxicant (otherwise, one would expect more mutagenesis). This may contribute to carcinogenesis, but it is not the MOA for carcinogenesis". This is overstated. It is not clear to me how can one say this with such certainty, particularly after describing the many possible mechanisms involved in arsenic carcinogenicity, and noting that inorganic arsenic can cause DNA and chromosomal damage. I would delete that last phrase "but it is not the MOA for carinogenesis".

4. Page 30, Table 1.This is a table of possible mechanisms of indirect genotoxicity. I note that oxidative DNA damage produced by ROS induced by As is not on the table. Is this considered by the Panel to be an indirect or a direct genotoxicity? Dose-dependent formation of 8-OHdG was observed in mammalian cells (human-hamster hybrid) by Kessel et al (2002). This was inhibited by both catalase and SOD. It is unclear that this study (and others by Hei's group at Columbia, Liu et al, 2001, 2005) were considered by the Panel in their discussion of arsenic genotoxicity. It is also unclear whether the Panel considers ROS-induced oxidative DNA damage to be direct or indirect genotoxicity and whether this type of genotoxicity should reflect a linear or nonlinear dose-response. (my opinion is that it should be considered to have a linear dose-response function).

5. Page 36. There is overspeculation on the potential benefits of arsenic hormesis. Line 29-30 states that at low levels (which is not defined) inorganic As may improve vascularization of normal tissues. No evidence is presented that this is the case, and thus it appears rather speculative. The text correctly goes on to note that promoting vascularization can be detrimental for atherosclerosis and tumor growth – this is not speculation as tumor growth is dependent on angiogenesis. On page 36 lines 37-38 and 37, line 1, the advisory states that if inorganic As is essential or hormetic, then a threshold "is certain". There is no reason to believe that a compound which may have certain benefits cannot also be a carcinogen with a linear dose-response function. The essentiality or potential hormetic effects, if any, are not necessarily linked to carcinogenesis. Further, a chemical that is hormetic for one life-stage (adults) may not have that same effect at a different lifestage (e.g., a developing fetus, infant, child). There is much evidence for serious health effects from arsenic and no evidence to speak of that there are hormetic effects in humans. In my opinion, that statement should be struck.

6. Section 3.4.2 was well written and I agree that the EPA should be looking at other epidemiological studies before finalizing the risk estimates for arsenic.

   On page 44, lines 5-24, some discussion of whether childhood exposure to inorganic arsenic is more problematic than exposure as adults is presented. This could be improved in two ways. First there are several studies now that suggest decrements in IQ from early life exposure to arsenic. These could be mentioned along with the discussion of adverse birth outcomes. Secondly, the recent paper by Allan Smith (Smith et al, 2006) clearly demonstrates an increased sensitivity to arsenic carcinogenesis (and As-induced bronchiectasis) when exposure occurs *in utero* and in childhood versus during adulthood. While more study is needed, this study should be added to the EPA document and to the Advisory. It is a well-conducted analysis and provides evidence for increased susceptibility to arsenic in early life. Furthermore, the statement on line 6 and 7 should be amended to indicate there is some evidence that children are more susceptible than adults to arsenic induced carcinogenicity. And, in the executive summary, this study result should be mentioned on page 8.

7. Page 46 line 18-22 again downplays DNA damage from ROS induced by DMA and arsenite exposure. I believe that the kinetics of DMA^V (e.g., lack of metabolism to inorganic arsenic in mammalian tissues) is the main argument that there is likely a nonlinear dose-response. The text indicates the SAB panel eliminated ROS-induced DNA damage as a "key event" for DMA. There are two concerns I have. One is that it is not clear from this advisory how the SAB committee decided what is a "key event" and what is not. How do you weight multiple mechanisms? There should be some explanation somewhere about this. Secondly it seems like the advisory relies on the assumption that ROS formation is nonlinear, which might (or might not) be true for DMA, and is less so for inorganic arsenic. As part of the explanation of "nonlinearity" for ROS-induced DNA damage, the text states that oxidative DNA damage repair enzymes protect

the genome and that these repair processes are expected to be nonlinear. I don't really know what is meant by the repair processes are nonlinear. But more importantly, DNA repair is not perfect; hence DNA damage can produce tumors. It is not clear to me that this argument is useful.

8. Section 3.5.4 Discussion of drinking water rates. Based on data from NHANES and CSFII, infants and children and pregnant women drink more water than nonpregnant adults on a body weight basis. Thus, while potency estimates should evaluate drinking water rates of the populations in the epidemiology studies, the EPA should consider drinking water rates of highly exposed individuals when evaluating risk from arsenic in drinking water. I realize this is a separate step in risk assessment than the estimate of potency, but it may be worth mentioning somewhere in this advisory.

Some typos:

p.31, line 23 seems to have a couple extra words ("a Chinese" before chromosome 1 in V 79 cells.)

p.36, line 23 dimethylbenzanthracene is misspelled.

p. 46 line 14-18, the sentence structure needs repair.

p.49, line 22, extra space in relationship.

9. Dr. Michael McFarland

In general, the SAB Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic was well written, concise and provided specific recommendations for ensuring that the best science is utilized by the Agency in assessing the human health risks associated with Dimethylarsinic Acid (DMA) and inorganic arsenic. The report furnishes full and complete responses to each of the Agency charge questions and, where appropriate, the Panel provides supplemental information and recommendations that the Agency should consider in establishing the carcinogenic human health risks associated with organic and inorganic arsenic. The following are my specific comments regarding the report.

The cover letter provides a clear and unambiguous summary of the salient points found in the body of the report. The Panel provides a clear rationale for their support of several Agency recommendations including the use of bladder tumor data from DMA rat bioassays for human cancer risk assessment, application of Taiwan epidemiological data as the basis for human cancer risks associated with inorganic arsenic as well as the use of the low dose non-linear extrapolation approach (and use of uncertainty factors to capture variability and interspecies differences) for estimating the cancer risks associated with DMA.

The Executive Summary was well written and provides a clear synopsis of the Panel's findings and recommendations from the body of the report. Information found in the Executive Summary was effectively distilled and presented in the cover letter. The Panel is applauded for highlighting many of the key uncertainties associated with extrapolation of current animal data sets for use in modeling the potential carcinogenic effects of DMA and inorganic arsenic in humans. The Panel is also commended for its encouragement of the Agency to conduct sensitivity analyses to evaluate the performance of arsenic cancer risk models.

The body of the report provides well written and comprehensive responses to the Agency charge questions. In crafting its responses to charge questions, the Panel furnishes cogent and scientifically defensible arguments in support and, in some cases, opposition to the Agency's position on specific science issues. Moreover, where appropriate, the Panel cites extensive peer-reviewed references that support its consensus findings and recommendations.

10. Dr. Granger Morgan

My apologies for being slow. I have now had occasion to read the SAB panel report "Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic."

While I am not an expert in this science, it is clear to me that this Advisory has involved an enormous amount to effort and that the panel has done a very thorough job. The report is clear and well written. By my reading it systematically responds to all of the charge questions.

In a number of places the report quite appropriately calls for sensitivity analysis. In most of these cases, such as the bottom of page 49 where the authors call for a comparison of a linear and non-linear dose response function, the value of such an analysis is very apparent. In a few cases, however, it sounded to me as if the models involved were all linear, so that the insight obtained from a sensitivity analysis would amount to just estimating the local slope of the output. Of course, that is worth knowing, but presumable is rather simple to obtain.

While EPA did not ask the panel, I could not help wonder if there are obvious research efforts that could dramatically improve our state of understanding. For example, are there populations (e.g in Bangladesh) that have been exposed to high levels of arsenic in drinking water but have yet to be studied? Given the enormous level of effort the panel has already devoted to this work, I would not ask them to produce a comprehensive outline of future research opportunities. At the same time. if in some of the specific discussions there are obvious studies, which if conducted might dramatically improve our knowledge, it would be appropriate to mention them.

I think a bit of clarification could help in lines 4-11 of page 2 of the cover letter which read:

"The SAB Panel supported the Agency's conclusion that on the basis of available data, human exposure to iAs appears to result in a wider spectrum of active metabolites compared to the expected metabolic profile from exposure to DMAV. Hence, the Panel agreed with the Agency that, in the absence of human data on DMAV, the bladder tumor data from DMAV rat bioassays is better suited for cancer risk assessment than is epidemiology data from iAs exposure. The Panel, however, noted that there remain significant uncertainties associated with the use of animal data for cancer risk assessment for DMAV due to the observed metabolic differences between rats and humans."

A reader not familiar with the field may find the argument that "iAs appears to result in a wider spectrum of active metabolites compared to the expected metabolic profile from exposure to DMAV" but, despite this fact one should use "the bladder tumor data from DMAV rat bioassays" rather than "epidemiology data from iAs exposure." Having read the report I think I understand the argument being made, but some clarification of the chain of logic in this sentence would be good.

In the letter on page 2 line 13 lets replace "MOA" with "mode of action."

Throughout the report the word "data" is treated as plural as it should be. I noted only two exceptions, both in the executive summary. On page 7 line 27

"…though the data has considerable limitations that should be described qualitatively or quantitatively to help inform risk managers about the strength of the conclusions."

Might better read:

"…though the data entail [or have] considerable limitations that should be described qualitatively or quantitatively to help inform risk managers about the strength of the conclusions."

Again on page 8 line 3"

"Much of the US and many other populations differ from the Taiwanese population of interest in factors that might influence the application of that data to the assessment of U.S. bladder cancer risks associated with inorganic arsenic."

Should read:

"Much of the US and many other populations differ from the Taiwanese population of interest in factors that might influence the application of those data to the assessment of U.S. bladder cancer risks associated with inorganic arsenic."

11. Dr. Rebecca Parkin

Here are my brief comments.

a) The report effectively responds to the charge questions. I was surprised, however, that the key statement made on p. 28, lines 29-30 does not appear in the Executive Summary. On reading the Summary before the text, I wondered whether Question B2 had been answered.

b) The report is clear and logical. It is full of technical information, but is well-organized and easy to follow.

c) The reviewers' rationale is documented, and level of documentation is appropriate to support the conclusions drawn.

Additionally, the discussion of drinking water consumption data and rationale for using particular data is excellent.

12. Dr. Joan Rose

The report was excellent and very well referenced. I have only a few comments for clarification.

1. The issue of the inputs to the risk and the overall/relative uncertainty and variability in the estimates could be more clearly described up front. It does not seem that drinking water intake (between 1 and 4 liters) is that which really influences the uncertainty of the risk output. Is cumulative dose an issue? [duration of exposure], non-linear relationships seem to key as well as low-dose extrapolation; interspecies extrapolation. Is there a way to contrast these uncertainties?
2. The sensitive populations regarding age for the carcinogenic risk of DVA^V seems to warrant more attention.

13. Dr. Stephen Roberts

Overall, I found the SAB report to be responsive to the charge questions, and the conclusions to be logical and supported by information in the body of the report. There were a few aspects of the report that could be improved, however, in my opinion. These are outlined in the comments below.

Pg. 18, lines 14-15, "… we do not expect to find significant amounts of MMA or iAs as products of DMA^V metabolism …": It would be helpful to include a statement about empirical evidence available to support this contention (e.g., measurements of MMA and iAs in tissues or urine after DMA administration). If empirical evidence is lacking, this should be acknowledged.

Pg. 22, lines 36-37, "This uncertainty should be properly addressed in the risk assessment for DMA^V exposure in humans.": Addressed how? This statement would be more helpful if accompanied by more explicit direction or at least an example.

Pg. 26, line 6, "Rather, the MOA is likely to be sustained cytotoxicity followed by genomic instability as a result of stress-related proliferation." The report lacks a clear articulation of the experimental evidence that supports this MOA. What appears in this paragraph reads more like a hypothetical construct. Later in the paragraph, the report states (lines 13-14), "In the case of arsenite, this would involve such factors as (See also section 3.3.3)." but it is unclear why observations with arsenite are necessarily relevant to the MOA for DMA^V bladder tumors in rats.

Pg. 31, lines 4-5, "... cause chromosome breakage, possibly mediated by ROS-induced DNA strand breaks.": Other sections conclude pretty strongly that ROS are not involved in the MOA for DMA^V. Does this statement contradict those statements elsewhere?

Pg. 37, line 24, "This question indirectly raises the issue as to the largest source for uncertainty for DMA^V risk assessment – conventional interspecies extrapolation or extrapolation across various forms of arsenic.": The report then follows with a list of various uncertainties. There is one uncertainty that doesn't seem to be contemplated in the report – namely, the possibility that *in addition* to an MOA based on repetitive cytotoxicity that gives rise to bladder tumors in rats, DMA^V also shares the MOA(s) of iAs that produce cancer in humans. As the report notes, there are no epidemiological studies of DMA^V exposure in humans with which to evaluate this possibility, and studies in rats are not particularly informative since they don't respond to iAs in conventional bioassays. There is room to speculate that DMA^V doesn't share the iAs MOAs (e.g., because of the diminished spectrum of arsenic metabolites from DMA^V compared with iAs exposure), but it is only speculation because the iAs MOAs are not clearly defined. This uncertainty should have been addressed in the report.

Pg. 38, lines 21 -22, "… laboratory animal studies have shown that DMA^V is not absorbed well – approximately 80% of a dose of the parent compound is excreted in a short time after exposure …": The two statements appear contradictory. Excretion of 80% of a dose shortly after administration, unless the dose is injected, suggests extensive absorption.

Pg. 45, lines 31- : Unpublished data are cited here to support an argument concerning linear versus non-linear approaches. Previously in the report (pg. 39), data from Gur et al. were mentioned in another context, with the statement that these data "… were never published and thus cannot be critically evaluated by the Panel. … Reliance on these studies would be stronger if the studies had the benefit of peer review." This gives the appearance of inconsistent standards regarding the acceptability of unpublished data in the SAB review.

<u>Minor editorial comments</u>:

Pg. 7, lines 6-7: Suggest revising to read " … in the Panel's complete response to charge question C1." That will make it clearer to the reader to look elsewhere in the document for these details.

Pg. 9, line 7: Delete "differences" at the end of the line.

Pg 27, line17, "The MOA outlined above …": Which MOA? The previous sections describe different possible MOAs.

Pg. 44, line 17: Suggest removing the comma after "µg/L"

Pg. 45, lines 13-15: It would be helpful to refer the reader to the previous section where the rationale for this statement (i.e., the rejection of ROS-induced DNA damage in the MOA for DMA^V carcinogenesis) is provided.

14. Dr. Thomas Theis

(a) Answer to the charge
In general the Panel has responded to the charge questions thoroughly and completely. Because of my background I focus more directly on the questions under "D" because these relate more directly to issues of uncertainty, variability, precision, and accuracy (as related to low-dose extrapolation). Each of the charge D1 through D5 request that the Panel comment specifically on some aspect of these factors; D1 deals with incorporation of uncertainty, D2 with the most appropriate type of extrapolation to use, D3 with precision and accuracy of the NRC model, D4 with drinking water intake value, and D5 food intake value. The Panel responses to D1 and D2 are clearly responsive to the charge. For D3, D4, and D5 the responses, while framed in a very thorough manner, generally take the form of a commentary on what needs to be done before these questions can be answered (instead of answering the questions as asked).

For D3 the Panel found errors in the model, and made several good suggestions for improvement, but did not directly assess its accuracy and precision. It may be that such an assessment is not at present possible; if so then perhaps a statement to that effect could be made.

D4 asks the Panel to recommend a drinking water intake value based upon the Taiwanese data. Again the Panel pointed out additional needs in this area, including the incorporation of variability parameters, sensitivity analyses, distinguishing consumption by sex, and the need to include other As sources.

For D5 the Panel's again recommends more sensitivity analyses related to dietary intake.

All of these are good suggestions. When coupled with the responses to D1 and D2 (which also recommend sensitivity analyses and MCA), the overall impression is that the Panel is not prepared, at this time, to recommend specific values for intake of As. It further suggests that uncertainty and variability of exposure and sensitivity of exposed sub-

populations will need to be factored into the ultimate recommendations. The Panel does not directly address the issue of variability in toxicological responses of an entire exposed population (preferring to focus on sensitive sub-populations as a way defining low-end exposure limits). In this context the Panel's approach does not challenge the Agency's preference against incorporating human toxicological uncertainty and variability into the analysis. One might argue that, by deriving standards based on variability in exposure parameters, and that are inclusive of the impacts on the most sensitive populations, the effect is similar. Perhaps so, but it would be a valuable exercise to compare standards derived in this way with those from a complete uncertainty analysis, inclusive of human toxicological responses.

(b) Clear and logical
Although I am not an expert in toxicology (and I defer to others on the Board with greater expertise on specific matters such as MOA and carcinogenesis) I found the report, in general, to be clear and readable. Knowing a bit about chemistry I found Figure 1 to be especially helpful.

(c) Supported conclusions
The Panel is to be commended for putting together a thoughtful, thorough, and scientifically defensible report. The conclusions appear sound, and the recommendations are supported by the accompanying material.

15. Dr. Valerie Thomas

The draft SAB arsenic review panel report addresses the original charge questions, and the conclusions and recommendations are supported by information in the body of the report.

In general the report is clear and logical. However, I find that the letter to the Administrator is not completely clear. Specifically, the paragraph on page 2, lines 4-19, could and should be rewritten so that it is easier to understand. The paragraph should make clear, perhaps by use of a heading, that it refers to the risk assessment of DMAv. In addition or alternatively, the paragraph would be more clear if the first sentence, lines 4-6, were simply cut. The detail is provided in the summary and the main text and does not need to be included in the letter to the Administrator.

16. Dr. Robert Twiss

All charge questions OK pending results of teleconference discussion

17. Dr. Lauren Zeise

The report is very well written and laid out and the Panel systematically addressed all of the original charge questions. The executive summary is an excellent synthesis of the

panel's position. However, as discussed below, there are areas of inconsistency in the report, and some conclusions are not fully supported.

Letter page 2, lines 22-23. With regard to inorganic arsenic (iAs), the letter states "The Panel also noted that the animal data does not suggest a linear response," without an indication of what studies support this claim. This statement is in general inconsistent with the available data and problematic as outlined below:

1) There are no standard positive bioassays with iAs, and indeed, reviews of carcinogenicity bioassays of arsenic have either maintained there is limited sensitivity in animals or no adequate bioassays run. It is problematic to indicate that the animal data do not suggest a linear response in the absence of an adequate cancer bioassay.
2) For the transplacental bioassays in mice of Waalkes et al. (2003), there are significant findings in male and female offspring treated during gestation at a number of sites (male - hepatocellular carcinoma, adrenal cortical tumors, lung; female – lung, ovarian), with only lung tumors in the female exhibiting substantial upward curvature.
3) With regard to the iAs metabolites, TMAO administered to male rats induced hepatocellular tumors with a linear dose response relationship. Dimethylarsenic acid exhibited non-linearity in the dose response for bladder carcinoma in male rats in the diet study, but in the drinking water study is consistent with linearity if the high dose group is not excluded. Subcutis fibroma increases were also consistent with linearity. The Panel does not suggest that the dose response assessment for iAs be based on the metabolite data.
4) Even if the shape of the dose response curve appeared non-linear and upward curving, the statement would still be problematic without additional clarification, because the thrust of the paragraph is addressing the assumption of linearity in the low dose region. Various genotoxic carcinogens have studies exhibiting non-linear response relationships but are consistent with linear responses in the low dose region (e.g., studies for dimethylnitrosamine, 2-AAF, formaldehyde, various forms of radiation).

Page 19, lines 6-7. In stating the extent that humans transform DMA to $TMA^{V}O$ and other trimethyl arsenic compounds care should be taken to indicate the extent to which it had been looked for, could have been detected, and the number of study subjects examined. The only direct study of TMAO after DMA exposure is the study Marafante et al. 1987 on one human subject (about 4% excreted as TMAO). The study of Buchet on human volunteers exposed to DMA did not analyze for TMAO, so no TMAO would be found. Because significant interindividual variability in metabolism may be expected (e.g., Vahter, 1999), care should be taken in generalizing the result from a single individual to the general public.

Page 19, lines 10-14 argues that the relative lack of $TMA^{V/III}$ "metabolites in human urine compared to rats "would suggest that the outcome in humans would not be as severe as in rats" for DMA. The reasoning is unclear. It is the DMA bladder tumors in the rat that is the focus of the dose response assessment (although subcutis fibromas are also observed, and in sensitive or transgenic mice lung and skin tumors and lymphoma). In the rat, the trimethyl form that was studied and found tumorigenic was TMAO, which caused

hepatocellular adenoma. If part of the argument is an hypothesized potential for TMA^{III}, a metabolite of TMAO, to damage DNA to a substantially greater extent than DMA^{III} and that humans are unlikely to produce trimethyl compounds to the same extent as the rat, that should be discussed. But again, the degree to which there may be sensitive groups within the human population that may transform DMA to trimethyl compounds is not known, and that should be presented as an important caveat if the argument is used. The Panel calls for study to determine whether the absence of TMA metabolites in humans is associated with decreased susceptibility to the carcinogenic effects of DMA^{V}.

Page 19, beginning at line 28. The Panel acknowledges the capacity of intestinal bacteria to demethylate arsenicals, and the possible spectrum of metabolites that may result in exposed individuals. It also notes the potential complications this may pose for cross species extrapolation. Also, the potential role of other microbial metabolites in DMA induced rat bladder cancer has been raised (Kuroda et al., Toxicol Appl Pharm, 2004, 198:345). This issue was not addressed in the uncertainty discussion on page 47.

On page 22, at lines 22 and 23 the Panel indicates that using the data from the DMA rodent study "may be the most reasonable approach" and then at lines 26-38, the Panel discusses the considerable uncertainty associated with the EPA's approach to DMA dose response modeling, and on line 36 calls for the Agency to address it properly in its risk assessment. However, this is not picked up later in the discussion of uncertainties in response to charge question D1 on page 47.

The Panel carefully considers the possibility of ROS and other mechanisms of potential indirect and direct mechanisms, and discusses a number of uncertainties. It states that "generation of low levels of oxidants from enzymatic sources or possibly by uncoupling of mitochondrial oxidations (if DMA^{V} can act in a matter similar to arsenate) may contribute to effects on cell signaling and transcriptional activation, as well as increase oxidant DNA damage." But ultimately the Panel finds that without continual cytotoxicity the tumorigenic response would not occur. The extent to which this holds for humans in the general population depends on the ongoing processes for bladder carcinogenesis in the general population and the extent the various components involved in DMA carcinogenesis may add to them. Bladder cancer is relatively common, with lifetime probability of contracting the disease for males at 4%. The extent to which the various possible mechanisms for DMA are involved in human carcinogenesis will depend on the background levels of these mechanisms from other exogenous and endogenous exposures.

In discussing the possibility of possible modes besides cell proliferation for DMA induced rat bladder cancer, the Panel does not include or discuss the possibility that TMA^{III} may contribute via a genotoxic mechanism. Elsewhere the Panel raises the possibility in hypothesizing that the rat may be more sensitive than the human because it forms considerably more trimethyl compounds after exposure to DMA.

In discussing the human relevance of the animal MOA for DMA the possibility that DMA is involved in human bladder cancer induced by iAs is not discussed. This seems

peculiar. Humans exposed to iAs produce considerable amounts of DMA and recent work has identified DMA ^{III} in human urine samples. DMA is the only one of the iAs metabolites tested that produces bladder cancer in laboratory animals. The concentration levels that bladder cancers are seen in humans are considerably lower than those seen in the rat, but considerably greater numbers of humans are captured in the epidemiologic studies. Actually, quantitatively, the results are fairly consistent if one allows for a linear term in the rat dose response relationship, at least for use in comparisons with the observations of bladder cancer in the human epidemiology. A possible role of DMA and its metabolites in the induction of bladder cancer observed in human studies deserves discussion, even if ultimately the Panel finds it unlikely.

In hypothesizing that rat data overestimate the human risk for bladder cancer because of greater production of TMAO and possibly TMA in the rat, it should be acknowledged that the extent of these compounds are formed in exposed humans is not known, and the potential for human variability deserves a mention.

The possibility of a threshold for chemicals that induce genotoxicity by a mechanism other than covalently binding with DNA is discussed on the bottom of page 29 in terms of a single hit theory. It is stated that a minimal concentration of agent would be needed. An important point that is not introduced into the discussion is the need to consider whether for any of the particular mechanism listed there are population thresholds because of concomitant exposures to other endogenous and exogenous agents and processes that affect the same mechanism. The issue of background additivity is also not addressed in considering the evidence for non-linearity of DMA in section 3.5.1.1.

In discussing the potential human relevance of the Waalkes transplacental carcinogenesis studies in mice, where in utero exposure lead to lung and liver tumors, recent epidemiological findings could also be noted. A study in Chile where large exposures to arsenic via drinking water occurred over a limited period, enabling study of its effects in different age windows, relatively large relative risks (RR = 6.1) were observed for lung cancer in those exposed in utero and early childhood (Smith et al., EHP, 114:1293, 2006).

At the bottom of page 36 is a discussion of the possible beneficial or essential effects of arsenic and it is stated that if in fact these are the case than a threshold is certain. This does not necessarily follow. While a chemical may be beneficial for some effects while at the same time having a negative effect on a different endpoint. These are not mutually exclusive. Fueling angiogenesis can both promote tumor growth and reduce cardiovascular risk. Further, as noted above, the issue of threshold needs to be considered in the context of the prevalence of the ill effect in the general population and the extent to which exposures to the agent in question add ongoing exposures and pathological processes.

On pages 39 and 48, on the basis of comparisons of in vitro LC50s for human and rat urothelial cell lines to DMA and arsenite and the Panel argues that the pharmacodynamic factor for interspecies differences could be reduced to one. The Panel does not provide a clear understanding how this translates to in vivo responses and how other factors

involved in bladder carcinogenesis may differ across the two species, such as in vivo exposure-time-response relationships for arsenic induced urothelial toxicity, differences in animal lifespans and the impact of the differences of the number of human versus rat cells available for insult. It is therefore unclear how one can conclude from short term in vitro measures of effect doses that the median human exposed for a lifetime will have exactly the same carcinogenic response to animals when exposed to the same internal dose as animals in the chronic bioassay. Another uncertainty raised in other parts of the Panel's report that were not discussed in response to the scientific uncertainty charge question D1 beginning on page 47 include the demethylation of DMA by intestinal bacteria.

There is also the nagging concern regarding the DMA assessment that iAs produces bladder cancer in humans drinking arsenic contaminated water and several human drinking water studies show that a considerable amount of ingested iAs is excreted in humans as DMA^{III}. The possibility that bladder induced cancer from iAs is due to DMA and hence the approach to low dose extrapolation is not sufficiently conservative given the observations of bladder cancers in humans at relatively low iAs concentrations needs to be addressed in response to charge question D1.

There is also the issue of other possible tumor sites. In the main DMA bioassay, subcutis fibroma was increased, and in studies in sensitive species or transgenic animals, tumors of the lung and skin and lymphoma was observed. This raises the possibility that DMA may contribute to cancer at sites other than the bladder, another uncertainty that could be discussed in response to charge question D1.

On page 44, the issue regarding whether epidemiological studies provide the basis for assessing the impact of childhood exposure. The recent study by Smith et al., mentioned above, which found large relative risks for lung cancer and very large risks for mortality from bronchiectasis – Relative risk of 46 – for in utero and early childhood exposure should be included.

Page 18, line 24. Ogra and Suzuki 2001 is not in the list of references
Page 18, line 24. Valenzuela 2005 should be Valenzuela et al. 2005
Page 24, line 12. "This may contribute to carcinogenesis, but it is not the MOA for carcinogenesis." This seems a peculiar requirement for MOA; there can be multiple modes of action, even for the same site. A similar statement also appears on page 33, at line 33.
Page 32, line 37. There was a review earlier this year by the NAS as part of its BEIR series for ionizing radiation, including dose response relationships for repair. Ultimately the committee concluded there would be linearity in the low dose range. This citation could be given. (Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 (2006), Board on Radiation Effects Research).
Reference page 15. Full reference for Smith et al 2001 is needed.