

**Summary Minutes of the US Environmental Protection Agency  
Science Advisory Board Arsenic Review Panel  
Public Conference Call Meeting Occurring on the Following Dates:  
Tuesday, January 24, 2006; February 23, 2006 and February 28, 2006**

**ARP Members:** See Roster – Attachment A

**Date and Time:** Tuesday, January 24, 2006  
Thursday, February 23, 2006  
Tuesday, February 28, 2006

**Location:** Telephone Conference Meetings Only

**Purpose:** The purpose of these meetings was to discuss Panel Member comments on the December 27, 2005 draft *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: An Advisory Report of the US EPA Science Advisory Board* (See Attachment B - [www.epa.gov/sab/pdf/arsenic\\_12-27-2005\\_dft\\_for\\_jan-24-2006.pdf](http://www.epa.gov/sab/pdf/arsenic_12-27-2005_dft_for_jan-24-2006.pdf); and Attachment C - [www.epa.gov/sab/pdf/arsenic\\_draft\\_12-27-05\\_comments\\_plus\\_note.pdf](http://www.epa.gov/sab/pdf/arsenic_draft_12-27-05_comments_plus_note.pdf)). Extracts of Member Comments are in an embedded comment summary (Attachment D; [www.epa.gov/sab/pdf/embedded\\_comment\\_summary\\_for\\_122705\\_dft\\_plu\\_note.pdf](http://www.epa.gov/sab/pdf/embedded_comment_summary_for_122705_dft_plu_note.pdf) and a compilation of member comments (Attachment E; [www.epa.gov/sab/pdf/compilation\\_arp\\_comts\\_on\\_dft\\_2\\_plus\\_note.pdf](http://www.epa.gov/sab/pdf/compilation_arp_comts_on_dft_2_plus_note.pdf)). The meetings were announced in the *Federal Register* (See Attachment F1 - 70 FR 76451, December 27, 2005 <http://www.epa.gov/fedrgstr/EPA-SAB/2005/December/Day-27/sab7850.htm>; Attachment F2 – 71 FR 6478, February 8, 2006 <http://www.epa.gov/fedrgstr/EPA-SAB/2006/February/Day-08/sab1721.htm>). Agendas for the meetings are in Attachments G1 - [www.epa.gov/sab/06agendas/arsenic\\_rev\\_panel\\_01-24-2006\\_agenda.pdf](http://www.epa.gov/sab/06agendas/arsenic_rev_panel_01-24-2006_agenda.pdf), G2 - [http://www.epa.gov/sab/06agendas/arsenic\\_rev\\_panel\\_02-23-2006\\_agenda.pdf](http://www.epa.gov/sab/06agendas/arsenic_rev_panel_02-23-2006_agenda.pdf), and G3 - [http://www.epa.gov/sab/06agendas/arsenic\\_rev\\_panel\\_02-28-2006\\_agenda.pdf](http://www.epa.gov/sab/06agendas/arsenic_rev_panel_02-28-2006_agenda.pdf).

**Panel Members Participating:**

<b>January 24, 2006</b>	<b>February 23, 2006</b>	<b>February 28, 2006</b>
<b>Chair:</b> Genevieve Matanoski <b>Panel Members:</b> Vas Aposhian Aaron Barchowsky David Brusick Kenneth Cantor John Colford Sioban Harlow Steven Heeringa Claudia Maria Hopenhayn James Klaunig Michele Medinsky Kenneth Portier Barry Rosen Toby Rossman Miroslav Styblo Justin Teeguraden Michale Waalkes Janice Yager	<b>Chair:</b> Genevieve Matanoski <b>Panel Members:</b> Vas Aposhian Aaron Barchowsky David Brusick Kenneth Cantor John Colford Sidney Green Sioban Harlow Steve Heeringa James Klaunig Chris Le Michele Medinsky Kenneth Portier Barry Rosen Toby Rossman Miroslav Styblo Justin Teeguraden Michael Waalkes Janice Yager	<b>Chair:</b> Genevieve Matanoski <b>Panel Members:</b> Vas Aposhian Aaron Barchowsky David Brusick Kenneth Cantor John Colford Sidney Green Sioban Harlow Claudia Hopenhayn Steve Heeringa Chris Le Kenneth Portier Barry Rosen Toby Rossman Miroslav Styblo Justin Teeguraden Michael Waalkes Janice Yager

**Others Attending:** See Attachment H

**MEETING SUMMARY:** The meeting was held over three separate telephone conferences in order to discuss and edit the draft report. The dates were January 24, 2006, February 23, 2006 and February 28, 2006.

**Tuesday, January 24, 2006**

**1. Thomas Miller, USEPA SAB ARP Designated Federal Office** convened the meeting. He reminded all participants and observers that the meeting was an open advisory meeting of the SAB under the auspices and requirements of the Federal Advisory Committee Act. He noted that the Panel members continue to comply with the regulations pertaining to FACA and EPA policies on advisory committees in its work and in addition they are required to follow the Federal Ethics and Conflict of Interest regulations and policies that apply to Special Government Employees.

Mr. Miller stated that the Panel’s work for the meeting was to edit and finalize its draft report to the Administrator in response to EPA’s charge ([www.epa.gov/sab/pdf/arsenic\\_review\\_panel\\_final\\_charge\\_7-25-05.pdf](http://www.epa.gov/sab/pdf/arsenic_review_panel_final_charge_7-25-05.pdf)). Mr. Miller noted that several persons had asked for time to make oral statements.

He then turned the meeting over to the ARP Chair, Dr. Genevieve Matanoski to carry out the agenda.

**2. Dr. Matanoski** noted that the Panel needed to discuss the remaining editorial, and several substantive issues, and complete its discussions so the draft report could be completed and sent to the Chartered SAB for review and approval. She reminded members that the focus of the report was to be science and that if policy issues were raised they needed to be clearly identified as such in the Panel's advice. She then asked for members of the public who had registered to make brief oral statements.

### **3. Public Comments:**

- a. Dr. Gary Kayajanian:** (Representing himself) (See Attachment I1 and [www.epa.gov/sab/pdf/kayajania\\_combined\\_post\\_913.pdf](http://www.epa.gov/sab/pdf/kayajania_combined_post_913.pdf) and I2-[http://www.epa.gov/sab/pdf/kayajanian\\_commentary\\_01-10-2006.pdf](http://www.epa.gov/sab/pdf/kayajanian_commentary_01-10-2006.pdf)). Dr. Kayajanian comments referred to the "J-shaped" curve that his analysis shows to be associated with inorganic arsenic studies done in Taiwan.
- b. Dr. Steven Lamm:** (Representing Consultants in Epidemiology and Occupational Health, Inc., see Attachments J - [www.epa.gov/sab/pdf/lamm\\_091305\\_arsenic\\_response.pdf](http://www.epa.gov/sab/pdf/lamm_091305_arsenic_response.pdf), K - [http://www.epa.gov/sab/pdf/lamm\\_10-05-05\\_arsenic.pdf](http://www.epa.gov/sab/pdf/lamm_10-05-05_arsenic.pdf), and L - [http://www.epa.gov/sab/pdf/hopenhayn\\_response\\_to\\_lamm\\_10-5-05.pdf](http://www.epa.gov/sab/pdf/hopenhayn_response_to_lamm_10-5-05.pdf) - Panelist response to Dr. Lamm). Dr. Lamm's comments focused on his reanalysis of the Southwest Taiwan dataset on inorganic arsenic.
- c. Dr. Joyce Tsuji:** (Exponent, Inc. representing the American Chemistry Council, Biocides Workgroup). (See Attachment M - [http://www.epa.gov/sab/pdf/shah\\_01-17-06\\_cover\\_tsuji.pdf](http://www.epa.gov/sab/pdf/shah_01-17-06_cover_tsuji.pdf), and Attachment N - [http://www.epa.gov/sab/pdf/01-17-06\\_tsuji\\_comments.pdf](http://www.epa.gov/sab/pdf/01-17-06_tsuji_comments.pdf)). Dr. Tsuji's comments focused on several factors she believes are relevant to inorganic arsenic's dose-response relationship and water intake rates relevant to arsenic dose-response analysis.
- d. Dr. Kenneth Brown:** (Representing the Treated Wood Council) (see Attachment O - [http://www.epa.gov/sab/pdf/kbrown\\_arsenic\\_submission\\_to\\_epa\\_1-16-06.pdf](http://www.epa.gov/sab/pdf/kbrown_arsenic_submission_to_epa_1-16-06.pdf); Attachment P - [http://www.epa.gov/sab/pdf/twc\\_miller\\_add\\_comments\\_epa\\_arsenic\\_10-20-05.pdf](http://www.epa.gov/sab/pdf/twc_miller_add_comments_epa_arsenic_10-20-05.pdf); and Attachment Q - [http://www.epa.gov/sab/pdf/kbrown\\_addit\\_comments\\_arsenic\\_sab10-19-05.pdf](http://www.epa.gov/sab/pdf/kbrown_addit_comments_arsenic_sab10-19-05.pdf)). Dr. Brown's comments focus on statistical modeling and interpretation of dose-response in the assessment of the S.W. Taiwan data.
- e. Dr. Samuel Cohen:** (University of Nebraska) Dr. Cohen noted the lack of demethylation by gastrointestinal microflora in studies in his laboratory. He also believes that the evidence points to non-linear possibilities for inorganic arsenic's dose response.

- f. **Dr. Pamela Mink:** (Exponent, Inc. Representing the Wood Preservative Science Council). (see written comments and materials from Dr. Mink and Dr. Jim Hale in the following: Attachment R - [http://www.epa.gov/sab/pdf/hale\\_request\\_for\\_time\\_01-17-06.pdf](http://www.epa.gov/sab/pdf/hale_request_for_time_01-17-06.pdf); Attachment S - [http://www.epa.gov/sab/pdf/comments\\_on\\_sab\\_draft\\_report\\_mink\\_01-17-06.pdf](http://www.epa.gov/sab/pdf/comments_on_sab_draft_report_mink_01-17-06.pdf); Attachment T - [http://www.epa.gov/sab/pdf/wpsc\\_hale\\_1-oct-6-2005.pdf](http://www.epa.gov/sab/pdf/wpsc_hale_1-oct-6-2005.pdf); Attachment U - [http://www.epa.gov/sab/pdf/wpsc\\_hale\\_2\\_oct-6-2005.pdf](http://www.epa.gov/sab/pdf/wpsc_hale_2_oct-6-2005.pdf); and Attachment V - [http://www.epa.gov/sab/pdf/wpsc\\_mink\\_follow-up\\_comments\\_10-20-05.pdf](http://www.epa.gov/sab/pdf/wpsc_mink_follow-up_comments_10-20-05.pdf))
- g. **Dr. Barbara Beck** (Gradient, Inc.; Representing the MAA Research Task Force). Dr. Beck's comments focused on arsenic dose-response modeling and the possible use of an MOE process for evaluating arsenic risk at exposures seen by the U.S. population.
- h. A written comment was also received from **Dr. Joshua Hamilton.** (Dartmouth Medical School, Representing himself) (see Attachment W - [http://www.epa.gov/sab/pdf/dr\\_j\\_hamilton\\_arsenic\\_comments.pdf](http://www.epa.gov/sab/pdf/dr_j_hamilton_arsenic_comments.pdf)). Dr. Hamilton's comments focus on mechanism of action, low dose extrapolation, and essentiality.
- i. **EPA Comments:** Several involved EPA staff persons thanked the panel for its efforts to date and noted their suggestions already discussed would be helpful to EPA. Dr. Lowitt noted that on page 21 and page 32 of the draft the document refers to a 10X FQPA safety factor. She noted that the actual factors that the discussion should be referring to were not from the FQPA rather, they were the 10X intraspecies and 10X interspecies extrapolation defaults. The report needs to make this clear.

#### **4. Arsenic Review Panel Discussions (A1, A2, B1, B2, B3):**

- a) **Arsenic Terminology:** Prior to discussing specific charge questions, the Chair led a discussion of several overarching issues:
  - i) **Policy:** The EPA SAB charter notes that the Board is to focus on the science that is used by EPA to develop policies and support decisions. Thus, the Panel should try as much as possible to focus its comments on science issues. That said, it is often the case that science and policy is not easily separated. Thus, it is possible that the Panel might advise on science in a way that moves into the policy area. In such cases, the Panel should do so with a clear recognition that it is doing so and it should acknowledge the fact in its report.
  - ii) **Support for Conclusions/Recommendations:** In discharging its review responsibilities for the Panel's draft report, the Chartered SAB will be looking for clear rationales for conclusions and

recommendations in the Panel report. Please ensure that your report sections do this in a clear way.

- iii) Arsenic Terminology: The current draft report uses a variety of ways to identify a specific arsenical. Often, it is not clear what arsenical is being referred to. The report sections should use a common terminology. The Panel discussed a draft “schema” for inorganic arsenic metabolism that suggests a set of terms that could be used to standardize the terminology in the report. After some clarifying discussions, the Panel agreed to use this schema and the terms it incorporates. This will be noted in the next draft of the report and the schema will be added.

- b) **Absence of Data, Research, and its Relationship to Evidence**: Members noted that the discussions of arsenic effects often are articulated in terms of there being “no data” indicating one factor or another. However, the document is often not clear if this is because 1) the issue has not been studied, or 2) the issue has been studied and the factor was not observed in the study. The Report sections should be clear about this when such statements are made and research recommendations should be made when appropriate.
- c) **Report Section 3.2.1 (Charge Question A1)**: Charge question A1 applies to metabolism and pharmacokinetics and EPA’s Charge stated that the efficiency of methylation reactions and cellular uptake varies with the arsenical compound administered. A one-way pathway is suggested for DMA<sup>V</sup> and significant amounts of [inorganic arsenic<sup>III</sup>], [inorganic arsenic<sup>V</sup>], MMA<sup>III</sup> or MMA<sup>V</sup> are not expected at target tissues. Charge Question A1: Comment on how PK [pharmacokinetic] information from direct DMA<sup>V</sup> exposure vs direct [inorganic arsenic] exposure is best considered in Risk Assessment.

Dr. Miroslav Styblo led the writing team on Charge questions A1 and A2 and he led the meeting discussions of the comments from members on these questions in the December 27, 2006 draft report (see Attachments C, D, and E).

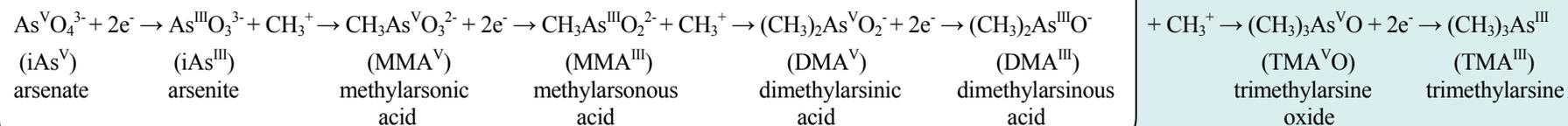
**Comment:** Some Panelists suggested that the report should say more about microbial degradation. After discussion, the Panel agreed that the report should include Dr. Styblo’s expanded statement (p. 12 lines 2-6) and that the report should emphasize the uncertainty associated with the issue because of an absence of data. Dr. Rosen’s reference to the PNAS article will be added to the document as will a call for additional research on the issue.

**Comment:** Dr. Le asked that the citation to his report be removed (Le, 2000) because it does not show DMA<sup>III</sup> to be a major urinary metabolite (page 13, paragraph 1). The citation will be retained and the word “major” will be removed from the text on page 13 lines 7 and 36.

## Schema of Inorganic Arsenic Metabolism in the Rat and Human

Rat

Human



**Comment:** Dr. Teeguarden's request to expand the PBPK discussion to include how it helps us to understand MOA was dropped by Dr. Teeguarden (page 15).

**d) Report Section 3.2.2 (Charge Question A2):** Charge question A2 applies to Mixtures of Metabolites and EPA's Charge stated that Tumor profiles vary with arsenicals administered. There are larger mixtures of metabolites after [inorganic arsenic] exposure than after DMA<sup>V</sup> exposure. Charge Question A2: Comment on the use, in DMA<sup>V</sup> assessment, of data derived from rodent exposures to organic arsenicals vs. data derived from direct [inorganic arsenic] human exposure.

**Comment:** Several Panelists noted discomfort with the wording "...this panel has no choice, but to recommend..." on line5-6 on page 16. Members pointed out that this is often the case in risk assessment that data indicating a problem are available from rodent data. The EPA document has a paragraph discussing these problems. Dr. Teeguarden will provide a brief introduction to this topic noting this common problem with the bases for quantitative risk assessment.

**Comment:** One Panelist noted that on page 15, line 42 through page 16 line 6, there is a discussion suggesting "significant" co-exposure to inorganic arsenic in drinking water, food and the environment. Dr. Rosen will provide a brief statement noting that this is often a problem in such studies. The word significant will be dropped.

**e) Report Section 3.3 Mode of Carcinogenic Action for DMA<sup>V</sup> and Inorganic Arsenic – (Charge Questions B1, B2, and B3):** Charge questions B1 through B3 address modes of carcinogenic action.

Dr. Toby Rossman led the writing team on Charge questions B1, B2, and B3 and she led the meeting discussions of Member comments on these questions in the December 27, 2006 draft report (see Attachments C, D, and E).

**i) Charge Question B1:** EPA's document states that in relying on laboratory animal data they make two critical assumptions. One is that data on animal tumors can be used to predict human cancers and two that animal tumor effects observed in studies conducted at high doses predict human risk at lower exposures. EPA states that an understanding of the mode of carcinogenic action can help inform them on how to assess risk and that for DMA<sup>V</sup> mode of action data were available and evaluated using the framework described in EPA's cancer guidelines. Charge Question B1 asks the SAB to "... comment on the sufficiency of evidence to establish the animal mode of carcinogenic action for DMA<sup>V</sup>. Are the scientific conclusions sound and consistent with the available evidence on DMA<sup>V</sup> and the current state of knowledge for chemical carcinogenesis." The question also asks the SAB to "...comment on whether the key events

in DMA's mode of action are supported by the available data..." Specifically comment on the role of: a) reactive oxygen species in producing chromosomal damage and the strength of the evidence supporting oxidative damage as a causal key event in DMA<sup>V</sup>/DMA<sup>III</sup>'s mode of carcinogenic action versus an associative event or a secondary consequence of cytotoxicity; b) cell proliferation and cytotoxicity and the strength of the evidence as causal key events in DMA<sup>V</sup>/DMA<sup>III</sup>'s mode of carcinogenic action versus associative or secondary events, and c) other potential modes of action that have substantial scientific support that may be contributing to the carcinogenicity of DMA."

**Comment:** Dr. Rossman started the discussion by referring to what she characterized as a very large misunderstanding which she attempted to resolve in her email of January 23, 2006 titled "Comments on Comments" (see Attachment X1 and X2). The misunderstanding was not whether oxidant stress may play a role in DMA<sup>V</sup> induced bladder cancer. She discussed a number of such ways that ROS may contribute. The issue is whether EPA's proposed mechanism of action (MOA) postulating DMA<sup>III</sup> induced oxidative DNA damage as the driving force in carcinogenesis by killing cells and by increasing mutagenesis or clastogenesis is correct. That mode disregards signal transduction, mutator phenotypes, and other ROS damage. Members discussed the need for more clarity in the section on page 18-19 of the December 27 draft to point out the cytotoxicity role vs. ROS damage to DNA. Panelists agreed that Dr. Rossman's "Comments on Comments" discussion would be integrated into the discussion to clarify the issue.

**ii) Charge Question B2:** EPA states that "There are little or no scientific data to suggest that if sufficient DMA<sup>III</sup> were present, key precursor events and ultimately tumor formation would not occur in humans directly exposed to DMA<sup>V</sup>" (USEPA, 2005a) Charge Question B2 asks the SAB to "...comment on the relevance of the postulated key events (see B1) to tumors in humans." It also asks the SAB to "...comment on how, if at all, differences in the human population vs. experimental animals should be accounted for in the risk assessment for DMA<sup>V</sup>."

**Comment:** Dr. Rossman noted that the second paragraph in this section is confusing in that it assumes that TMA<sup>III</sup> is present in the rat bladder. Panelists agreed with the need to clarify the paragraph.

**Comment:** Paragraph 3 of the section (page 21 of December 27 markup) makes a brief statement regarding whether the young are at greater or lesser risk from arsenic exposure than adults. Panelists agreed to clarify whether this is an issue of absence of studies or an absence of effects in existing studies.

**iii) Charge Question B3:** EPA states that, “Inorganic arsenic (iAs) undergoes successive methylation steps in humans, resulting in the intermediate production of  $iAs^{III}$ ,  $MMA^V$ ,  $MMA^{III}$ ,  $DMA^V$ , and  $DMA^{III}$ . Each arsenical metabolite exhibits its own toxicity.” Charge Question B3 asks the SAB to “...comment on the conclusion that the available data support the hypothesis that multiple modes of action may be operational following exposure to inorganic arsenic.”

**Comment:** Panelists discussed the statement on page 22 referring to the small number of studies that found genotoxic activity in rodent studies. The paragraph may oversimplify the issue. A lengthy discussion was conducted on the issue of whether arsenic could be considered either as 1) a compound in which “direct damage to DNA is involved – through ROS - - and thus low dose effects are likely to be linear” or 2) one in which other processes that are not understood completely are involved, and thus the effects are likely to be non-linear. The issue is important to EPA because that simple categorization can determine the way in which EPA will handle risk predictions. Thus, the ROS issue needs to be clear in terms of whether it is not accepted as a key event because adequate study shows this to be the case or whether there has not been sufficient study to demonstrate its role. If it is a lack of study issue, then EPA may default to an assumption of linear. Panelists agreed to clarify by adding a paragraph that enlarges on the existing paragraph and gives a more recent coverage of genotoxicity and reflects the complexity of the issue.

**Comment:** Panelists discussed the issue of micronuclei production observed in epidemiology studies and micronuclei in general. Panelists agreed to clarify this issue.

**Comment:** The draft report discusses arsenic hormesis and essentiality issues noting pros and cons. Some Panelists noted their discomfort with suggesting arsenic is essential or beneficial. The issue should not be eliminated from the document but it should be clear that though we are discussing the issue, we are not supporting arsenic essentiality. Hormesis is often discussed with radiation exposures, but it is an artifact. Panelists agreed to retain a discussion and to ensure that any conclusions are supported by evidence.

The meeting was adjourned and the DFO stated that he would survey members of their next availability to continue to execute this agenda and complete the discussion of questions that have not yet been discussed (i.e., charge questions C and D).

## **Thursday, February 23, 2006, Reconvene the Meeting**

**1. Thomas Miller, Designated Federal Officer** for the SAB Arsenic Review Panel convened the meeting and reminded members and the public of the FACA requirements that structure SAB activities and the ethics requirements that Panel Members serve under. He reminded persons on the call to mute their phones unless they were speaking and to not place their phones on hold as that usually interjects extraneous sounds into the call. He introduced the Chair, Dr. Matanoski, who reminded all of the need to stick to the published agenda and complete the Panel discussions on the issues on that agenda. She noted that public statements will be taken in the concluding session of this meeting which is to be held on February 28, 2006.

### **2. Arsenic Review Panel Discussions of February 23 (C1, D3, D4, D5)**

**a) Report Section 3.4.1. Animal Data for DMA<sup>V</sup> Dose-Response (Charge Question C1):** EPA stated that, “A number of different rodent bioassays (standard bioassay, transgenic animals, susceptible rodent strains, initiation and promotion studies) are available on DMA<sup>V</sup>” Charge Question C1 asks the SAB to “...comment on the use of the bladder tumor data from the DMA<sup>V</sup> rat bioassay as the most suitable dataset for quantifying potential human cancer risk to DMA<sup>V</sup>, including the weight of evidence to support this conclusion.”

Dr. Michele Medinsky led the writing team on Charge question C1 and she led the discussion of the comments from members on this section of the draft report (see Attachment C, D, and E). Dr. Medinsky provided a draft response to the comments made on this section of the report and this draft formed the basis for the discussions of the section during the conference call.

**Comment:** A Panel Member suggested referring to section 3.2.1 in paragraph 2 of this section of C1 (p 25), and that the language in C1 may also help clarify the similar discussion in A2 (p 16). Dr. Medinsky suggested adding the cross reference in the section and the Panel Members agreed.

Dr. Yager suggested that we add to this section a suggestion that EPA also consider an ILSI framework for the relevance of rodent data in risk assessment. The Panel members agreed to addition of such a statement.

**Comment:** A Panel Member noted that the qualitative judgment made in characterizing rat urinary bladder tumors as “low grade” transitional cell papillomas in contrast to human UB tumors as “high grade” invasive transitional cell carcinomas is not one of qualitative substance. Dr. Medinsky proposed deleting the following sentences (page 26, lines 10 to 14 in the draft): “...Human bladder tumors are primarily transitional cell carcinomas, and rat bladder tumors are reported to bear some similarity in pathology to low-grade papillary tumors that occur in humans; however,

they are not similar to invasive human bladder tumors that display high grade malignancy (Cohen, 2002). The foregoing, taken together, illustrate known substantial metabolic,..." Panel members agreed with the deletion.

Members also considered whether the wording stating that rats are "... considerably more sensitive... than humans" needed to be revised to something like "may be more sensitive". There is much uncertainty on this issue. The discussion should consider evidence suggesting more sensitive (e.g., longer half-life, etc.) – the Panel should call on EPA to do more research and to explain the issue better. The Panel agreed and Dr. Teeguarden was asked to provide draft language on the issue.

**Comment:** A member suggested rewording the statement on DMA<sup>III</sup> production after DMA<sup>V</sup> exposure (Page 26, lines 37-40) noting that there are no studies on this issue rather existing studies are on DMA<sup>III</sup> production after iAs exposure. Members agreed to clarify this as follows (the underlined portion is to be deleted):

"A second major uncertainty associated with using bladder tumor data from rats is the lack of knowledge about levels of DMA<sup>III</sup> that might be produced in the human bladder upon exposure to DMA<sup>V</sup> and how those levels would compare to levels of DMA<sup>III</sup> produced in rats exposed to DMA<sup>V</sup>. The few human exposure studies that exist seem to indicate little if any DMA<sup>III</sup> production takes place after exposure to inorganic As. Laboratory animal studies have shown that DMA<sup>V</sup> is not absorbed well ---approximately 80% of a dose of the parent compound is excreted in a short time after exposure (Buchet, et al., 1981; Marafante, E., et al., 1987). Additionally, rat urothelial cells are 3.5 times more sensitive to DMA<sup>III</sup> than are human urothelial cells in *in vitro* studies (Cohen, et al., 2000).

**Comment:** A Panel member suggested rewording the statement in paragraph 5 under C1 noting that there is no direct evidence showing rats to be more sensitive than humans in carcinogenic response after DMA<sup>V</sup> exposure (p 27).

**Comment:** The statement regarding the FQPA Safety Factor reduction needs to be clear that it applies to DMA's pesticide use and that a reduction would be an Agency policy call and choice. In addition the statements in this section regarding potential reductions in the PK vs. PD components of the factor generally contradict the discussion in D1 (p 27).

Dr. Teeguarden raised the rat-human pharmacokinetics issue noting that the bar is high regarding the amount of support needed to claim a significant difference in rat-human PK. We need sufficient information on

rat and human PK to say for a given unit dose of DMA<sup>V</sup> you get a certain concentration of DMA<sup>III</sup>. We can suggest a difference but more research could give better support for the premise. For pharmacodynamics, the bar may not be so high and it is reasonable to suggest to EPA that it might consider a change to PD.

Dr. Medinsky suggested some additions and deletions (deletions are underlined). Further, the reference to the FQPA was deleted and the words “interspecies safety factor s” substituted. She asked for more information regarding the strength of the evidence for reduction of safety factors for the toxicokinetic and toxicodynamic portions of the safety factor.

“Suggested Revision: These toxicokinetic and toxicodynamic factors should be taken into account in the application of rat bladder tumor data to assess human bladder cancer risk and the selection of safety factors. These factors will impact the choice of uncertainty factors since the weight of evidence indicates that the rat is considerably more sensitive to bladder tumor induction from direct exposure to DMA<sup>V</sup> than are humans. Although selection of a safety factor is the province of EPA’s policy choice, the Panel believes that in the case of the interspecies safety factor for this element of risk assessment, the science supporting a smaller factor could lead EPA to choose to lower the factor for arsenic to some number less than 10. The increased sensitivity of rats relative to humans could be taken into account. The Arsenic Review Panel’s analysis of the toxicokinetic data indicates that an uncertainty factor for extrapolation from rat toxicokinetic data to human risk in this case is likely to be less than one. The analysis of the toxicodynamic data indicates that the uncertainty factor may also be lower than the default. The application of safety factors has also been addressed in the Panel’s response to question D1.”

**Comment:** A Panel member asked for clarification of the rat vs. human bladder tumor development issue relative to the time lag. The statement does not refute the utility of rodent data for human risk predictions. The pattern in humans seems to be the same – late development. (p 27). The implication of the statement is that there is a difference in arsenic induced bladder tumors and bladder tumors in humans. That is not the case because these tumors also occur late in life in humans. Humans and rats are similar in that regard. Dr. Medinsky proposed additions and deletions (deletions are underlined in the following) to do this and Panel Members agreed to this and the preceding two comments.

“The Agency should also discuss in its Science Issue Paper, similarities and differences between rats and humans in the development of bladder tumors, and how these differences impact interspecies extrapolation. For

example, urinary bladder tumors in rats occur very late in life. Studies suggest that in rats it takes two or more years of continuous high dose exposure to DMA<sup>V</sup> to induce these tumors. This would equate to a human being developing cancer very late in life as well. The Science Issue Paper should specifically discuss the similarities and differences in the time for induction of DMA<sup>V</sup> related tumors in rats with the pattern observed with humans and arsenic associated urinary bladder cancer.

**Comment:** A Panel Member asked for clarification of the terms “non-specific induction of tumors” (p 28). Dr. Medinsky proposed to delete the term “non-specific.” Panel Members agreed.

**Comment:** A Panel Member suggested adding information on co-carcinogenesis to the discussion on C3H mouse carcinogenicity. (p 28) Dr. Medinsky suggested that Dr. Waalkes and Dr. Rossman edit the paragraph. Dr. Rossman’s revisions to charge question B will be useful in the co-carcinogenicity discussion. Dr. Waalkes will provide revisions on the discussion on “spontaneous” tumor occurrence in this strain. During the discussion, he noted that recent data shows that arsenic is a transplacental carcinogen in CD1 mice, a strain that does not show a high rate of spontaneous tumor development. Members agreed to these members providing the revisions.

There were no comments on Charge Question C1B.

**b) Report Section 3.5.3. EPA Model Re-implementation (Charge Question D3):** EPA stated that they had “...re-implemented the model presented in the NRC (2001) in the language R as well as in an Excel spreadsheet format. In addition, extensive testing of the resulting code was conducted.” Charge Question D3 asked the SAB to “...comment upon precision and accuracy of the re-implementation of the model.”

Dr. Steve Heeringa led the writing team on this charge question and he led the discussion of the comments from Panel Members on this question during the telephone call meeting (see Attachments C, D, and E). Dr. Heeringa noted the Panel had identified several issues that may be of consequence to EPA’s assessment.

**Comment:** The issue of male-female imbalance in the population seems problematic. Follow up information from Dr. Heeringa explains the situation and could be added here (see the compilation of member comments on the second draft of the report). Dr. Heeringa noted that information he had been provided showed that the information in the EPA report, though unusual, was accurate. He suggested deleting the gender imbalance remark from the section. The Panel Members agreed with the change.

**Comment:** He noted that he had added a reference to Morales to the section. He stated that he had gone to the Issue Paper and noted that EPA attributed the data used in Bier.IV and MCCancerFirt.xls to the paper by Morales. He checked the information and confirmed that the data are drawn from that paper and has added a statement to that effect to the draft. Panel Members did not disagree.

**Comment:** Dr. Heeringa noted that the term in the first equation in D3 has been notation in formula (page 45) changed to “dose.” No disagreement was noted.

**Comment:** Dr. Heeringa stated that, in light of the sex-ratio issue discussed earlier, the comments from Drs. Matanoski and Harlow regarding the male-female imbalance, were resolved by deleting his earlier statement in the text. The Members agreed.

**Comment:** Dr. Heeringa discussed the comment he added on p 48 lines 15 -19 that referenced a comment in 3.4.2 regarding a practical approach to sensitivity analysis of the multiple well village issue. Should we repeat that information here? Some members thought it would be helpful and agreed to leave the inserted reference. Members discussed whether to be more specific in addressing the “extreme values” issue. Dr. Heeringa and Dr. Portier noted that they wished to stick to a more simplified approach of advising a sensitivity analysis and that EPA has the greatest familiarity with their model and should have a good sense of what to include in that analysis. Also, some members of the public have provided advice here that can be useful to EPA. Members agreed to the simplistic approach.

At this point in the meeting the call was interrupted by a participant that placed their phone on hold. The operator assisted and disconnected the line.

**Comment:** Dr. Heeringa discussed the note on page 48 line 26 where members indicated a need to examine sensitivity of the model to the assumption of zero arsenic exposure from food. The model discusses well water and drinking water assumptions, but not exposure via food and cooking water. He suggests discussing the details of this factor in the food and water sections. In this section the reference is to point out the lack of documentation for the assumption in the issue paper. Members agreed.

**Comment:** Dr. Heeringa noted that on page 48, line 35, the panel recommended a specific form of a model other than the additive and linear dose model that is implemented by EPA. The form recommended comes from NRC 2001. He noted that Morales actually deals with a variety of forms of the model. Dr. Heeringa noted that the recommendation as written may be too prescriptive of an exact form of a multiplicative and

linear model to consider in EPA's sensitivity analysis. He suggested editing to tell EPA to consider forms similar to this model from NRC 2001 to ensure comparability to that advice. For example to advise that EPA look at nonlinear models, including multiplicative and quadratic terms, as explored in Morales. NRC's point in this is to note that this form is among the best, but that it is not the only one to use. Members agreed.

**c) Report Section 3.5.4. Available literature describing drinking water consumption rates for the Southwestern Taiwanese study population: (Charge Question D4)** EPA stated that the "NRC recommended drinking water ingestion of 1 L/day for the US and two rates for Taiwan (1 L/day and 2.2 L/day). New studies are available on the issues. EPA suggests a rate between 1 and 4.6 L/day. Charge Question D4 asked the SAB, "What drinking water value does the panel recommend to use in deriving the cancer slope factor for iAs?"

Dr. Sioban Harlow led the writing team on Charge Question D4 and she led the discussion of the comments from members on this section of the December 27, 2005 draft report (see Attachments C, D, and E).

The discussion was brief and Dr. Harlow noted that no comments beyond her own asking about using extremes of the range were in the draft. One member noted that the Panel might provide extra information on the issue of beverages prepared using non-local sources of water. Dr. Harlow suggested that it might be best to keep the Panel's advice here non-prescriptive noting that the advice already suggested that EPA clarify these issues in its analyses. No changes were required for the section.

**d) Report Section 3.5.5. Selection of an estimate of Dietary Intake of Arsenic from Food. (Charge Question D5)** EPA stated that "NRC found that the ED01's sensitivity to changes in food intake from 50 to 30 micrograms per day changed the ED01 only about 1%. New studies exist and EPA currently models dietary intake for several levels. Charge Question D5 asked, "What background dietary intake value does the panel recommend for control and study populations in SW Taiwan for use in deriving the slope factor for iAs?"

Dr. Janice Yager led the writing team on Charge Question D5 and she led the discussion of the comments from members during the February 23, 2006 telephone conference meeting of the Panel.

Dr. Yager started the discussion by noting that the Issue Paper on page 20 states that studies from which food concentration rates in tables in EPA's assessment came from locations that differ from rates in Taiwan. This statement is not supported with quantitative or other types of information. The degree to which the Panel agrees with this assumption will weigh on what the Panel will say in this section. She asked that members keep this in mind as the discussion is conducted.

EPA also wanted advice on background dietary levels to be used for analysis of control population. Dr. Yager noted that the Panel had not yet addressed that and needed to do so—zero contribution from food is assumed in the current slope factor. She asked what range the panel would advise for the sensitivity analysis for D3 relative to the control population. There is background information for the U.S. population of 1.3 – 11.4 micrograms/day total arsenic. It is not clear if there are background data for areas outside the arsenic endemic area in Taiwan.

With that, Dr. Yager turned to specific comments.

**Comment:** Members discussed the suggestion that we not advise EPA to use extreme values in its sensitivity analysis (e.g., 200 micrograms per day for women and children). Members considered: i) whether the values noted were extreme; whether they reflected ranges or ranges of means; ii) the appropriate groupings of sex and age to use in the analysis relative to background in food; iii) background levels discussed in the NRC 2001 and NRC 1999 analyses; iv) whether sensitivity analysis is based on the individual or populations; and v) using a value below the dose calculated for Taiwan and determining how heavily this would influence the overall risk assessment.

Members agreed to revise the section to reflect the discussion. The section should: i) generalize the advice to imply EPA should do a population- based analysis; ii) cite a range of mean values from the literature that reflects population exposure and not to recommend one alone; and iii) cite U.S. background levels as published and suggest that as input for starting levels in the sensitivity analysis regarding control population levels. Dr. Yager will check the NRC 1999 and 2001 for more citations on this issue and to see if there are studies available on the dietary background intake for Taiwan outside the arsenic-endemic area and if none are found we will suggest using the US background as a starting point for sensitivity analysis on this issue and not assume zero.

**Comment:** A member suggested deleting or expanding the wording to better explain the statement “...on the basis of absolute risk as well as relative risk.” (page 53, line 5) The members agreed with the comment and the sentence will be modified to delete “absolute risk” and end with “on the basis of comparative relative risk”

**Comment:** Dr. Yager noted that there were several clarifications needed in the last paragraph on page 53. She will revise them according to the mark-up. Members agreed.

**Comment:** A member asked about the clarifications suggested in the markups on Page 52 lines 15 -19 and 29-31. Dr. Yager noted that the discussions on revising earlier sections will resolve these issues. The paragraph will be clarified according to those changes (e.g., derivation of slope, provide better documentation, and leave room for EPA to do population based sensitivity analysis). Members agreed.

The meeting was adjourned and the DFO stated that the Panel would reconvene and complete its discussions of C2, D1 and D2 on Tuesday, February 28, 2006. He noted that there would be oral statements by the public at that time as well.

### **Tuesday, February 28, 2006, Reconvene the Meeting**

**1. Convene: Thomas Miller, Designated Federal Officer** for the SAB Arsenic Review Panel convened the meeting and reminded members and the public of the FACA requirements that structure SAB activities and the ethics requirements that Panel Members serve under. He reminded persons on the call to mute their phones unless they were speaking and to not place their phones on hold as that usually interjects extraneous sounds into the call. He introduced the **Chair, Dr. Genevieve Matanoski**, who reminded all of the need to stick to the published agenda and complete the Panel discussions on the issues on that agenda. She noted that public statements will be taken in the concluding session of this meeting.

### **2. Arsenic Review Panel Discussions of February 28 (C2, D1, D2):**

**a) Report Section 3.4.2 Use of Human Epidemiological Data from Direct iAs Exposure (Charge Question C2):** EPA stated that additional US epidemiology studies have been conducted on inorganic arsenic in drinking water since the NRC 2001 report. Charge Question C2 asks it "...the SAB agrees that the Taiwanese data set is still the most appropriate for estimating human cancer risk?"

**Comment:** Members discussed the discrepancy in the number of villages with multiple wells (21 vs. 22) between page 30 and 31; whether the many past analyses and peer reviews of this (Taiwanese) data supports their strength; and the need to clarify the "reliability of exposure" statement and its relation to precision on page 30. The correct number is 22 villages with multiple wells. Members agreed to point out the large number of analyses and peer reviews of the data set as a strength and to clarify the "reliability of exposure" issue by referring to a long duration of exposure.

**Comment:** Members discussed the wording that ends paragraph 2 in C2 and suggested that the Panel point out that the Taiwanese data is not adequate for human risk assessment and that additional work is needed, even though the dataset still seems to be the most appropriate (p 30). The issue centered on use of the data set for estimating risk versus proof of causation. Members decided to revise the section but to retain the thought

that the dataset is the most appropriate for estimating risk at this time and to include further clarification of additional needs in succeeding paragraphs of the section.

**Comment:** Members discussed whether there is a need for stronger language than “be considered by EPA” and “...it should be possible” relative to use of other epidemiological data sets (p 31). Members agreed to clarify the issue, to link the discussion to other paragraphs in the section; to indicate that the additional data sets need to be critically evaluated; and to also refer to the need for sensitivity analyses.

**Comment:** Members discussed the lengthy insertion on “integrative analysis” (p 32-34). The material was not meant to be inserted as is rather to provide an example of where such analyses had been conducted. Members agreed to delete the inserted text and to replace it with a paragraph drafted by Dr. Yager and sent forth in her February 24, 2006 email (see Attachment Y) – and that specific edits would be made to parts of that paragraph (e.g., addressing bias and non-differential misclassification; that the approach be suggestive and not a firm approach that needs to be done only this way, that the Panel is not suggesting a new risk assessment paradigm, the need to have specific criteria for use in evaluating studies for inclusions in some integration (not a meta analysis), and how the approach may improve statistical power (not that it always results in such an improvement)).

Charge Question C2 – Part 2: asked if “...the data provide adequate characterization of the impact of childhood exposure to inorganic arsenic? Please discuss the rationale for your response.”

**Comment:** Members discussed rewording the last paragraph in C2 Part 2 on childhood exposure to inorganic arsenic. Members agreed to the rewording with edits and to accept an edit that introduces “smoking as young adults” as an issue.

**b) Report Section 3.5.1 Mode of Carcinogenic Action Understanding for DMA<sup>V</sup> and Implications for Dose Response (Charge Question D1):** EPA stated that the 2005 cancer guidelines focus on mode of action (MOA) and prefer a biologically based model for estimating risk. There is not sufficient data on DMA<sup>V</sup> to do this. Charge Question D1: Asks the SAB to comment on the evidence and biological rationale for nonlinear versus linear low dose extrapolation approaches for DMA<sup>V</sup>, and how uncertainty should be handled.

Dr. Justin Teegarden led the writing team on Charge Question D1 and he led the meeting discussion of the comments on the draft report during the Panel’s meeting (see Attachments C, D, and E).

**Comment:** The reference to B3 on line 36 of page 36 should be changed to B1.

**Comment:** Members discussed a clarification of the number of steps needed for carcinogenicity (earlier in the report, 3 steps were mentioned and in this section 2 are mentioned) (p. 36, Lines 38-40). This will be resolved by bringing this section of the report into conformance with the discussion in Charge Question B1.

**Comment:** (p. 37, Line 8) Members discussed modifications that would remove an overemphasis on the lack of support for the ROS key event. Dr. Teeguarden suggested that the Panel distinguish between three possibilities: 1) insufficient data to invoke ROS; 2) sufficiency of data to refute a role; and 3) a combination of both 1 and 2. The paragraph will be made consistent with the consensus on question B1.

**Comment:** (p. 37, Line 16-26) Additional clarifications are needed in the discussion of the postulated MOA and (p. 37 lines 21-22) the issue of the relationship between increased 8-oxo-dG and DMA) – this will be deleted. Members agreed that the postulated MOA will be identical to B1 or this section will simply refer to B1. Also members proposed that B1 include a bullet form MOA with key events identified.

**Comment:** (p. 37, lines 33-36): The reference to *in vitro* cytotoxicity in uroepithelial cells will be added and the data behind the statement will be confirmed as will its publication status (with Dr. Cohen).

**Comment:** (p. 37, Line 41) Members discussed the statement “Even the production of ROS and its interaction with DNA, a key event in the MOA postulated by OPP and ORD would be nonlinear functions of DMA dose.” The noted that it did not discuss DNA repair. The statement will be deleted.

**Comment:** Members discussed the need to include a discussion of DNA repair on page 38, Line 6. DNA repair will be added to this section.

**Comment:** Members held a lengthy discussion of clarifications needed in paragraphs 2 and 3 on page 38. It included discussions of ROS vs. genotoxicity and the role of DMA, direct interactions with DNA, the major role of cytotoxicity in DMA carcinogenicity, dose levels involved, the suggestion of the full process being non-linear (relative to risk estimation) if a component is non-linear, chromosomal aberrations, the position and approach that EPA would need to follow if the panel is not clear in its advice here, and whether DNA was a primary target of DMA. The section will be revised and its message will be consistent with that of

question B1 or it might be removed because it will be redundant with the discussions in that section.

**Comment:** Members discussed additional editorial needs for those parts of the ROS discussion on page 38 lines 40 through page 39 line 15. The text will be revised to note that these are examples of mechanisms and the discussion will be revised to remove the ROS portions of the sentences from lines 7 to 10 on page 39 and line 19. Again the need to make this consistent with question B1 was pointed out.

**Comment:** Dr. Teeguarden suggested deleting the paragraph in lines 21-34 on page 39. Members agreed it is redundant and can be deleted.

**Comment:** Members agreed to use the terms pharmacodynamics, pharmacokinetics and uncertainty factors.

**Comment:** On page 40, Lines 18-21, Members discussed available information on low dose extrapolation for DMA via linear and non-linear approaches and the need for additional research on MOA so that uncertainty can be better addressed.

**Comment:** On pages 40 and 41, the issue of uncertainty factor is discussed again in terms of its reduction and the notion that such a choice is the province of policy. The issue arises also in C1 and the reference to policy will be made consistent with the discussion in that section. Also, the notion of insufficient data on reducing the PK factor is retained here.

**c) Report Section 3.5.2 Implementation of the Recommendations of the NRC (2001) (Charge Question D2).** EPA stated that they have determined that for inorganic arsenic the most prudent approach to model cancer risk is to use a linear model because of significant remaining uncertainties in which iAs metabolites may be the ultimate carcinogenic moiety and how mixtures of metabolites interact at sites of action. Charge Question D2: asked, “Does the panel concur with selection of the linear model for iAs cancer risk at this time?”

Dr. Claudia Hopenhayn led the writing team on charge question D2 and she led the discussion on the section during the February 28, 2006 Panel session.

**Comment:** Members discussed the need for removing the reference to recent low dose studies as being inappropriate for a series of reasons common to such low dose epidemiology studies. Members agreed to keep the statement but to revise it to convey the ideas from the draft as relevant criticism to low dose epidemiological studies and to note that this introduces problems into using them for low dose extrapolation relative to larger higher-dose studies. Dr. Hopenhayn will revise the first paragraph and send it to the DFO.

The Chair noted that lead writers for each Charge question should revise their sections of the draft report according to the discussions in the January 24, February 23, and February 28, 2006 sessions of this panel meeting and to send them to the DFO for compilation into a revised draft that will be sent to panel members for review, comment and concurrence. Members should deliver their revisions to the DFO during mid-March, 2006.

### 3. Public Comments:

- a) **Dr. Steven Lamm (representing Consultants in Epidemiology and Occupational Health, Inc.)** discussed his analysis of the South Western Taiwanese data, confounders, aquifer data sources, an EHP paper from 2006 on township confounding issues, and made a recommendation for an integrated analysis.
- b) **Dr. Gary Kayajanian, (representing himself)** referred to his analysis of the Taiwanese data that shows benefits of arsenic below 50 micrograms per liter; the Utah data; and suggested that EPA erred in reading the data. He sees no reason to decrease the arsenic drinking water level to less than 25 micrograms per liter and suggested this as a case in which data are available and modeling is not necessary.
- c) **Dr. Ken Brown (representing the Treated Wood Council)** addressed the use of statistical measures of the quality of the proposed dose-response model and additional analytical issues for the Taiwanese data (see Attachment Z1).
- d) **Dr. Christine Chaisson (representing the American Chemistry Council, Biocides Panel Chromated Copper Arsenate Work Group)** addressed the use of defaults vs. contemporary standards suggesting the use of multiple models to inform decision making (see Attachment Z2).
- e) **Dr. Pamela Mink (representing the Wood Preservative Science Council)** addressed additional analysis needed for the Taiwanese data, the value of newer case-control and cohort studies, and integrated analysis. Her call was broken in audio quality and she was asked by the DFO to provide them in writing (see Attachment Z3).
- f) **Other Comments:** Several members of the public provided written comments to the panel:
  - i) **Dr. Barbara Beck** – Attachment Z4
  - ii) **Dr. Jim Hale, Wood Preservative Science Council** – Attachment Z5
  - iii) **Dr. Gary Kayajanian** – Attachment Z6
  - iv) **Dr. Steven Lamm** – Attachment Z7

Dr. Matanoski noted that revisions should be to the DFO by March 16, 2006. The DFO thanked the Panel and the Public and adjourned the meeting at 3:30 pm.

Respectfully submitted

*/ Signed /*

---

Thomas O. Miller  
Designated Federal Officer  
US EPA SAB Arsenic Review Panel

Certified as True:

*/ Signed /*

---

Dr. Genevieve Matanoski  
Chair  
US EPA SAB Arsenic Review Panel

#### **Attachments**

- A Arsenic Review Panel Roster
- B Dec 27, 2005 draft report – clean version
- C Dec 27, 2005 draft report with embedded comments from first circulation
- D Embedded comment summary
- E Compilation of Panel Member Comments on Dec 27 draft with embedded comments
- F1 FR Notice for January 24, 2006 ARP Telecon Meeting
- F2 FR Notice for February 23 and 28, ARP Telecon Meetings
- G1 Agenda for the January 24, 2006 Telecon Meeting of the ARP
- G2 Agenda for February 23, 2006 Telecon Meeting of the ARP
- G3 Agenda for February 28, 2006 Telecon Meeting of the ARP
- H List of Public Contacts with DFO on ARP Meetings Jan-Feb 2006
- I1 Dr. Kayajanian, Comments anti-carcinogenesis
- I2 Dr. Kayajanian, commentary on Dec 27, Draft on arsenic
- J Dr. Steven Lamm, CEOH, 9-13-2005, Response to statements at 9-13-2005 meeting
- K Dr. Steven Lamm, Georgetown University School of Medicine, Dept. of Pediatrics,  
10-5-2005 comment – Population Distribution by Gender and Age
- L Dr. Claudia Hopenhayn, comments on Lamm, 10-5-2005)
- M Dr. Hasmukh Shah, 1-17-2006, ACC CCA Workgroup re Dr. Tsuji
- N Dr. Joyce Tsuji, 1-17-2006, Comments on Dec 27 report, American Chemistry Council, Copper Chromated Arsenic Work Group
- O Dr. Kenneth Brown, 1-16-2006, Comments on Dec 27 report, Treated Wood Council
- P Mr. Jeffrey Miller, 10-20-2005, Treated Wood Council letter re Dr. Brown

- Q Dr. Kenneth Brown, 10-19-2005, Treated Wood Council Comments
- R Dr. Jim hale, 1-17-2006, Request for Oral Presentation and Written Comments,  
Wood Preservative Science Council
- S Dr. Pamela Mink, 1-17-2006, Comments on Dec 27 Draft report
- T Dr. Jim Hale, Las Vegas Review-Journal article on Fallon, NV
- U Dr. Jim Hale, 10-5-2005, Fallon, NV study
- V Dr. Pamela Mink, 10-20-2005, data for dose-response assessment
- W Dr. Joshua Hamilton, Dartmouth Medical School, MOA and extrapolation
- X1 Dr. Toby Rossman, email 1-23-2006, "Comments on Comments"
- X2 Dr. Toby Rossman, email 1-24-2006, Corrected Slides
- Y Dr. Janice Yager, email 2-24-2006, regarding C2
- Z1 Dr. Kenneth Brown, 2-28-2006 – Treated Wood Council
- Z2 Dr. Christine Chaisson, 3-2-2006 – American Chemistry Council Biocides Panel  
CCA Work Group
- Z3 Dr. Pamela Mink, 2-28-2006 – Wood Preservative Science Council
- Z4 Dr. Barbara Beck, 2-16-2006 – Gradient Corporation Comments
- Z5 Dr. Jim Hale, 2-17-2006 – Wood Preservative Science Council Comments
- Z6 Dr. Gary Kayajanian, 2-13-2006 - Hormesis
- Z7 Dr. Steven Lamm – Email 2-28-2006 – Withdrawal of previous comment