

**Summary Minutes of the  
US Environmental Protection Agency  
EPA Science Advisory Board  
Arsenic Review Panel  
Public Meeting  
Washington, DC**

**September 12-13, 2005**

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

**Date and Time:** Monday, September 12, and Tuesday, September 13, 2005 (See Attachment B (to Physical File) for the Federal Register notice for the meeting)

**Location:** Double Tree Hotel, 1515 Rhode Island Avenue, NW, Washington, DC

**Purpose:** The purpose of this meeting was for the Board to deliberate and to develop responses to EPA's charge on several issues associated with their analysis of arsenic's carcinogenic mode of action.

**Attendees:** Panel Chair: Dr. Genevieve Matanoski

Panel Members:

1. Dr. Genevieve Matanoski, Chair, Johns Hopkins University
2. Dr. H. Vasken Aposhian, University of Arizona
3. Dr. Aaron Barchowsky, University of Pittsburgh
4. Dr. David Brusick, Covance, Retired
5. Dr. Kenneth Cantor, National Cancer Institute
6. Dr. Jack Colford, University of California, Berkeley
7. Dr. Yvonne Dragan, National Center for Toxicological Research
8. Dr. Sidney Green, Howard University
9. Dr. Sioban Harlow, University of Michigan
10. Dr. Steven Heeringa, University of Michigan
11. Dr. Claudia Hopenhayn, University of Kentucky
12. Dr. James Klaunig, Indiana University
13. Dr. X. Chris Le, University of Alberta
14. Dr. Michelle Medinsky, Consultant
15. Dr. Kenneth Portier, University of Florida
16. Dr. Barry Rosen, Wayne State University
17. Dr. Toby Rossman, New York University
18. Dr. Justin Teegarden, Pacific Northwest National Laboratory
19. Dr. Miroslav Styblo, University of North Carolina
20. Dr. Michael Waalkes, National Cancer Institute
21. Dr. Janice Yager, Electric Power Research Institute

**Others Participating in the Call:** See Sign-in Sheets in Attachment C (to physical file)

## **Meeting Summary**

### **Monday, September 12, 2005**

The discussion followed the issues and general timing as presented in the meeting Agenda (Attachment D to physical file).

**A. Tom Miller - Convene the Meeting:** Mr. Thomas Miller, Designated Federal Officer for the SAB Arsenic Panel, convened the meeting and noted that this meeting was an open advisory meeting of the SAB under the auspices and requirements of the Federal Advisory Committee Act. This Panel charge and background documents, as well as public comments, are on the EPA websites at:

- 1) [http://www.epa.gov/sab/panels/arsenic\\_review\\_panel.htm](http://www.epa.gov/sab/panels/arsenic_review_panel.htm)
- 1) [http://www.epa.gov/oppsrrd1/reregistration/cacodylic\\_acid/](http://www.epa.gov/oppsrrd1/reregistration/cacodylic_acid/)
- 2) <http://www.epa.gov/waterscience/sab/>.

Mr. Miller noted that the Arsenic Review Panel (ARP) was formed using published SAB procedures and that documentation for the ARP are also on the SAB Website. He noted that a portion of this issue was determined to be a particular matter and that financial interests could be impacted by the issue. However, in regard to the Arsenic Review Panel, the Deputy Ethics Official for the SAB determined that the legal criteria for making a conflict of interest, or an appearance of impartiality, finding is not met. Mr. Miller reminded Panel Member that if issues arose during their participation in this SAB activity that might indicate a conflict or an appearance issue, they should inform me immediately so that we can consider the need for and nature of any appropriate remedy.

Mr. Miller noted that is EPA and SAB policy to allow for public input to the SAB that is relevant to its deliberations and that twelve persons had registered to present oral statements at this meeting.

Then Mr. Miller asked those on the Panel to introduce themselves by name and affiliation and they did so.

Mr. Miller introduced Dr. Vanessa Vu, SAB Staff Office Director to make a few comments.

**B . Dr. Vanessa Vu** welcomed everyone to the meeting and thanked all for sharing their time. She noted the importance of this work. She then introduced Dr. Matanoski.

**C. Dr. Genevieve Matanoski Comments:** Dr. Matanoski welcomed the participants and thanked them for agreeing to help with this activity. She discussed the approach for the meeting and noted that Subgroups of ARP members have been formed to address the specific issues in each charge question. She noted that the Panel's task was to respond to the questions (i.e., advising) and not to provide a critique of the EPA documents as would be the case if we were conducting a peer review of the full assessment. She stated that

completing the Panel's report might require some follow up telephone conference meetings.

Dr. Matanoski noted that during the public comment period that public presenters would each be allocated 10 minutes of time on the agenda, but that their presentations would be held to five minutes so that Panel Members could have an opportunity to ask questions of the presenters. The intent of your oral statements is to clarify your previously submitted written statements.

#### **D. Agency Presentations**

1) **Dr. William Wood US EPA, Office of Research and Development**  
(Attachment E to physical file): Dr. Wood discussed key features of the 2005 Cancer Guidelines with special emphasis on the treatment of Mode of Action information. Mode of Action is defined as "Key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer or other health endpoints." A key event is an "Empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element." Dr. Wood discussed the use of MOA information, the MOA framework, the two-step dose-response approach, the point of departure (the lowest point that is adequately supported by data), and quantitative dose-response assessment.

#### **Members Questions and Comments:**

a) How much internal EPA review occurred on EPA's MOA before it was made public? {There was considerable interaction via the Workgroup.}

2) **Dr. Vicki Dellarco, US EPA, Office of Pesticide Programs (OPP)**  
(Attachment F, part 1 to physical file): Dr. Dellarco discussed the mode of carcinogenic action for cacodylic acid and agency recommendations for dose response extrapolation. Dr. Dellarco noted that the motivation for OPP's assessment activity at this time is the Food Quality Protection Act (FQPA) requirement to conduct a safety review of all pesticide tolerances by August 2006. Dr. Dellarco discussed how EPA assesses risk and conducts its risk characterization activity noting that the 2005 Cancer Risk Assessment Guidelines require EPA to be transparent and clear about its assumptions and uncertainties in the assessment and how they affect it and that assessments must reach sound conclusions based on the best available science using generally accepted scientific principles and knowledge. She summarized the background and EPA's conclusions on 3 issues of importance to EPA's DMA assessment:

Issue 1) the dataset for estimating cancer risk associated with exposure to DMA.

Issue 2) the mode of action underlying rodent tumor response and its relevance to humans.

Issue 3) dose response extrapolation approach

3) **Dr. Anna Lowit, US EPA, Office of Pesticide Programs (OPP) (Attachment F, part 2 to physical file)**: Dr. Lowit discussed the issues that need to be considered in a dose response assessment and EPA's assessment for cacodylic acid. She noted that the guidelines describe a two-step dose response process which separates modeling the observable range of data and extrapolation to lower doses. Dr. Lowit discussed the Agency's considerations for selecting the point of departure noting EPA looked at the 1% and 10% benchmark responses and noted the importance of the benchmark response selected. Dr. Lowit noted the various dose response approaches considered for estimating risk from direct exposure to DMA. Finally, she summarized the EPA assessment's conclusions noting:

- a) the rat is a relevant model for DMA5 and provides the most complete dataset for cancer;
- b) the MOA is convincing and based on scientifically defensible key events which support nonlinearity, and
- c) aggregate exposure assessment will address multiple pathways of exposure to exogenous DMA5 residues.

**Members Questions and Comments (Dellarco and Lowit) focused on:**

- a) Reactive oxygen species in vivo or in vitro? {A written response was provided by Dr. S. Nesnow later in the day – see Attachment F2 in the physical file}
- b) Evidence for gene mutations?
- c) The existence of MOA relevant data in primates? Is there in vivo mutation data available?
- d) Research showing DMA<sup>V</sup> and MMA<sup>V</sup> as metabolic end products and EPA's focus on classical pathways for inorganic arsenic?
- e) Studies showing more consistency of MOA among rats and other species would increase the comfort in the proposed MOA. The existence of pharmacokinetic differences.
- f) The role of TMAO in DMA toxicity.

4) **Dr. Elizabeth Doyle, US EPA, Office of Water and Dr. Jonathan Chen, US EPA, Office of Pesticide Programs (See Attachment G)**: Dr. Doyle introduced the discussion noting that the existing IRIS inorganic arsenic cancer slope factor was based on skin and it was published in the 1960s. The National Research Council provided reports to EPA on inorganic arsenic in 1999 and 2001 that encouraged EPA to update this cancer slope factor.

Dr. Chen discussed information on the metabolism of inorganic arsenic. He noted that carcinogenic effects for inorganic arsenic have been shown in the skin, bladder, lung, liver, kidney, and prostate (human epidemiology) and for inorganic arsenic at very high doses in an animal model. Dr. Chen noted that the predominant metabolite from inorganic arsenic metabolism is DMA<sup>V</sup> and that it is

rapidly excreted; however, the amount excreted varies between species and among humans depending on a number of factors (e.g., nutrition, sex, age, life style, disease status, genetic status--polymorphism).

Dr. Chen proposed a number of reasons for EPA retaining the linear extrapolation approach for inorganic arsenic (E.g., multiple potential MOAs, metabolites have distinct toxicities, different factors affect the production of specific metabolites). He noted that EPA's charge asks for SAB comments on that conclusion that data support the hypothesis of multiple modes of action after inorganic arsenic exposure.

Dr. Chen noted that EPA evaluated numerous data sets in its assessment of inorganic arsenic. He discussed the reasons for why the Agency decided that the Southwestern Taiwan study (Chen et al., 1985 and Wu et al., 1989) was still considered to be the most useful data set for dose response assessment. He asked if the panel agreed that the Taiwanese dataset remains the most appropriate for estimating human cancer risk.

Dr. Chen discussed a number of dietary issues and differences among the Taiwanese exposure situation and the U.S. situation. Issues discussed included drinking water consumption rates, body weight differences, food consumption rates, and arsenic concentrations in food. He stated that variation due to food accounted for 2 – 9 percent of the risk attributed to inorganic arsenic. He asked the panel what background dietary intake levels they would suggest for use in evaluating the control and study population relative to the cancer slope factor.

Dr. Chen also discussed differences in U.S. and Taiwanese drinking water intake levels. He asked the panel for advice on the appropriate drinking water value to use in deriving the slope factor for inorganic arsenic.

Dr. Chen discussed EPA's reimplementation of the model for estimating cancer potency. He asked if the panel concurred with EPA's selection of the linear model and if it could comment on the precision and accuracy of the reimplementation.

**Members Questions and Comments focused on:**

- a) Why EPA had not considered polymorphism (Taiwan vis a vis U.S. populations)
- b) Salt reabsorption in the study populations
- c) Water ingestion via green tea ingestion,
- d) Differential arsenic levels in different areas where crops receive water having different levels of arsenic contamination.
- e) The reasons for why EPA and NRC models have different risk levels for bladder tumors.
- f) The rationale between gender differences in water ingestion in Taiwan vs the U.S.

g) Are other high-dose studies informing the EPA assessment other than Taiwan {Considered Chilean data but Taiwanese data are still the basis for EPA's assessment).

**5) Dr. William Farland, Acting Deputy Assistant Administrator for Science, US EPA Office of Research and Development** (see Attachment H): Dr. Farland presented an overview of the EPA documents and charge. He noted that the inorganic arsenic document is a cancer health assessment, and that the organic arsenic document is primarily an MOA analysis. The documents embody principles in the 2005 cancer guidelines and the SAB advice on DMA<sup>V</sup> will shape risk assessments for several other organic arsenicals.

Dr. Farland summarized the key points for the OPP and OW analyses and discussed in greater detail the risk assessment issues embedded in the EPA analyses:

- a) Use of human carcinogenesis for inorganic arsenic assessment and rat data for DMA<sup>V</sup> assessment;
- b) Evidence for a DMA<sup>V</sup> MOA;
- c) MOA and its implications for dose response assessment for both organic and inorganic arsenic; and
- d) Considerations for low-dose extrapolation for DMA<sup>V</sup> and inorganic arsenic in humans.

## **E. Public Comments**

Dr. Matanoski introduced the public comment session. She reminded commenters that each would have 10 minutes total for their interaction and that only five minutes should be allocated to presenting so that members would have an opportunity to ask them questions.

Prior to the meeting, all but three public commenters agreed to a reordering of the published agenda (see Attachment I in the physical file to reflect those in agreement with the change – numbers 3 through 11 on the revised list; other commenters, i.e., 1, 2, and 12 on the revised and original lists were not affected by the change in order). The Panel Chair agreed to allow this reordering in the interest of expediting the comment session.

1) **Dr. Gary Kayajanian, representing himself** (see Attachment J in the physical file for his written comments and presentation slides). Dr. Kayajanian commented on the need for EPA to use existing real data (e.g., Utah study) instead of modeled or extrapolated data in its assessment and his basis for concluding that arsenic is a potent anti-carcinogen.

2) **Dr. Rosalind Schoof, representing herself** (see Attachment K in the physical file for her presentation slides). Dr. Schoof commented on low levels of arsenic contamination of U.S. soils and the impact on health risk for arsenic at 50 ppm

and lower. She remarked on the need for small communities to make tradeoffs among arsenic drinking water treatment and other uses of public funds.

3) **Dr. John DeSesso, representing himself** (see Attachment L in the physical file for his written comments and presentation slides). Dr. DeSesso discussed developmental toxicity of arsenic and its relevance to sensitive life stages and the use of a 10X uncertainty factor to protect children from developmental toxicity.

4) **Dr. Kenneth Brown, representing the Treated Wood Council,** (see Attachment M in the physical file for his written comments and presentation slides). Dr. Brown discussed the modeling of U.S. cancer risk from inorganic arsenic and the Southwest Taiwan data relative to use in dose-response analysis.

5) **Dr. Steven Lamm, representing himself** (see Attachment N in the physical file for his written comments and presentation slides). Dr. Lamm discussed database selection for cancer risk estimation, the SW Taiwanese dataset, the use of epidemiological study datasets vs. ecological study datasets, the NE Taiwan data, and sources of outcome variability in each.

6) **Dr. Pamela Mink, for the Wood Preservative Science Council** (see Attachment O in the physical file for her written comments and presentation slides). Dr. Mink discussed the use of epidemiologic data to evaluate cancer risk, specifically her review and meta-analysis of low-level arsenic exposure in drinking water and bladder cancer.

7) **Dr. Joyce Tsuji, Exponent, representing the American Chemistry Council's Biocides Panel, Chromated Copper Arsenate Work Group** (see Attachment P in the physical file for her written comments and presentation slides). Dr. Tsuji discussed additional U.S. studies of carcinogenicity of inorganic arsenic, a recent meta-analysis of recent studies, and the SW Taiwanese data relative to arsenic exposures in the U.S.

8) **Dr. Samuel Cohen, University of Nebraska Medical Center, representing himself** (see Attachment Q in the physical file for his written comments and presentation slides). Dr. Cohen discussed research on the carcinogenic mode of action and dose-response for DMA and for inorganic arsenic, the role of cytotoxicity in DMA carcinogenicity, the unlikely role of oxidative damage to DNA in arsenic carcinogenicity, and the use of a margin of exposure extrapolation for humans.

9) **Dr. Elliot Gordon, Elliot Gordon Consulting, LLC, representing himself** (see Attachment R in the physical file for his written comments). Dr. Gordon discussed the use of sound science principles in responding to the charge questions from EPA.

**10) Dr. Barbara Beck, Gradient Corporation, representing the MMA Research Task Force** (see Attachment S in the physical file for her written comments and presentation slides). Dr. Beck discussed her recommendations for DMA assessment focusing on benchmark dose analysis, the Hill model, interspecies toxicokinetics and toxicodynamics, and safety factors. Dr. Beck obtained agreement from the Chair to also present the public comments of Dr. Jim Armbruster, PBI/Gordon, Inc. (see Attachment T in the physical file for these presentation slides). This presentation provided comments on cumulative assessment of MMA, DMA, and inorganic arsenic.

**11) Dr. Jennifer Sass, Natural Resources Defense Council, representing the NRDC** (see Attachment U in the physical file for her presentation slides). Dr. Sass discussed the NRC report (2001), the 2005 EPA cancer guidelines requirements, additional arsenic endpoints, and EPA's strategic goals for pesticides and other chemicals.

## **F. Discussion of Charge and Review Materials**

[NOTE: To be more meaningful, this section of the minutes will integrate the discussion points with the ultimate draft consensus statements from each charge-specific subgroup. During the meeting, each question was discussed in turn and then on the afternoon of day two of the meeting, the draft consensus statements were read aloud by each subgroup and revisions suggested.]

The charge to the SAB is in Attachment V to the physical file of these minutes. Attachment W is the Science Issue Paper: Mode of Carcinogenic Action for DMA. Attachment X is the Toxicological Review of Ingested Inorganic Arsenic. Attachment Y is the Issue Paper: Inorganic Arsenic Cancer Slope Factor 7/23/05 and Attachment Z is a Compilation of Premeeting Comments.

### **1) Issue A. Metabolism and Toxic Responses of Arsenic Species**

#### **A1) Metabolism and Pharmacokinetics:**

This discussion began with a presentation by Dr. X. Chris Le, ARP Member, on arsenic speciation. Dr. Le discussed methods for analysis of MMA and DMA, instability problems, uncharacterized arsenic species, and binding of trivalent arsenic metabolites and arsenic in the blood (see Attachment AA in the physical file for his presentation slides).

Member discussions mentioned the following: the comparability of DMA and MMA across sites and time; trivalent arsenic in cells in association with glutathione; exhaled breath as an excretion route; the assertion that arsenic metabolism is one way; differences in metabolism when DMA is administered vs. inorganic arsenic; DMA uptake; microbial metabolism of arsenic in the intestine; pharmacokinetics of DMA; and the role of nutritional state in arsenic uptake.

**Draft Consensus Remarks for A1. Metabolism and pharmacokinetics: Please comment on how pharmacokinetic processes are best considered regarding the use of data derived from direct DMA<sup>V</sup> exposure versus direct iAs exposure for cancer risk assessment.**

{Dr. Styblo for the Subgroup} DMA(V) from organoarsenic-containing herbicides is degraded by microorganisms in the environment to yield trimethylated, monomethylated and inorganic As species. It should be noted that this and the following questions deal only with exposure and metabolic fate of DMA(V) and do not address the degradation byproducts.

We agree with the Agency's reasoning behind this question. In mammalian (including human) tissues/cells, the metabolism of inorganic arsenic appears to be a one-way process in which inorganic As(iAs) is converted to mono-, di-, and trimethylated species containing As in +3 or +5 oxidation state. While the step-wise addition of methyl group is likely a one-way process, a cycling between +3 and +5 As species may occur at each of the methylation steps due to spontaneous oxidation of +3 species and non-enzymatic or enzymatic reduction of +5 species.

Given the one-way character of As methylation, we do not expect to find significant amounts of monomethylated or iAs as products of DMA(V) metabolism in either rat or human. On the other hand, exposure to iAs results in the production and tissue retention of all the above As species. The reduction of DMA(V) to DMA(III) is apparently a critical step in the activation of DMA(V). It is not clear, where and to what extent (if at all) it occurs in humans exposed to DMA(V). However, DMA(III) is a major urinary metabolite in individuals chronically exposed to iAs, indicating that the capacity to reduce DMA(V) to DMA(III) exists in human tissues. It should be pointed out that even a conversion of a small amount/fraction of exogenous DMA(V) to DMA(III) is of a toxicological significance due to a significant toxicity of DMA(III). Thus, strictly from the point of view of the metabolic pattern, data derived from DMA(V) exposure (in the Rat), not from iAs exposure, should be used for cancer risk assessment. However, there is a great deal of uncertainty associated with this approach. This is mainly due to the following metabolic differences and other factors:

1. The differences in the number and the amounts of DMA(V) metabolites in rats and humans (rat – DMA(V), DMA(III), TMA(V)O, and possibly, TMAs(III); human – DMA(V), DMA(III)). Because of specific chemical and toxicological properties of TMA(V)O and TMA(III), these metabolites are likely to affect the severity and character of toxic or cancerous outcomes in the rat as compared to human.
2. Retention of DMA(III) in rat erythrocytes (bound to Hb) contributes to specific kinetic pattern for DMA(V) in rats. It is not

clear how and to what extent this factor affects the yield and concentration of the active As species (DMA(III), TMA<sub>2</sub>O, or TMA<sub>3</sub>(III)) in target tissues.

3. Microorganisms, including intestinal bacteria, have a capacity to either methylate or demethylate DMA(V). Thus, oral exposure to DMA(V) may result in the absorption of a wide spectrum of As metabolites in GI tract of exposed individuals. This possibility should be considered in the risk assessment of DMA(V) exposure (e.g., the As species found in tissues may differ with different routes of exposure!).
4. Additional factors may affect the metabolic profiles for DMA(V) in humans, including co-exposures to other environmental contaminants, malnutrition (starvation has been shown to induce expression of AQPs – As transporters), or deficiencies of specific nutrients (e.g., Se).

A PBPK model would be the best approach for integrating tissue and excreta concentrations of As metabolites resulting from exposure to the various forms of As, including DMA(V), in laboratory animals and humans. This model can accurately simulate concentrations of an active (toxic or carcinogenic) metabolite(s) in urine and bladder following exposure to DMA(V). This approach could be used for dose response analysis in cancer risk assessment. Such model must be validated for predicting tissues concentrations of active species regardless of the source of As exposure.

There were no follow up discussions of these statements.

## **A2) Response to mixtures of metabolites:**

Member discussions mentioned the following: interspecies extrapolation and whether extrapolation from rodents to man or from inorganic arsenic to DMA gave the most uncertainty; exposure to many arsenicals with inorganic arsenic vs. just one with DMA; the dose of DMA needed to cause tumors in rats and doubt that such high doses could be achieved in humans; the uncertainty in which arsenic species might be the most toxic; uncertainty of risk estimates; the context provided by the FQPA relative to DMA risk assessment; whether a ten-fold safety factor relative to the noted uncertainty; cytotoxicity relative to carcinogenicity; whether human data existed to move away from use of rat data as normally done by EPA; and the potential for genotoxicity of arsenic species.

**Draft Consensus Remarks for A2. Response to mixtures of metabolites:** *Given the toxicological response profiles observed following direct exposures to iAs versus MMA<sup>v</sup> and DMA<sup>v</sup>, and the differences in human and rodent toxicologic responses to arsenicals, please comment on the use of data derived from rodent exposures to the organic*

*arsenicals versus use of data derived from direct iAs human exposure, in the DMA<sup>V</sup> assessment.*

{Dr. Styblo for the Subgroup} The answer to this question is essentially linked to the answer to the charge question A1. The metabolism of iAs yields a wide spectrum of metabolites some of which (iAs, MAs) are not produced in significant amounts during the metabolism of DMA(V). Both iAs and MAs metabolites have specific toxic properties, targets, and endpoints, which are absent in DMA(V) exposure in rats or humans. **Because there are no data on toxicological responses to DMA(V) in humans, we believe that data derived from rodent exposures should be used for the risk assessment in DMA(V) exposed individuals.**

However, a significant degree of uncertainty is associated with this approach due to metabolic differences between rats and humans and due to other factors, including those listed in A1. Specific toxicities of TMAs(V)O and TMAs(III) that are (may be) metabolites of DMAs(V) in rats, but not in humans, are of a particular concern to this panel. The role (or contribution) of these metabolites in the manifestation of toxic and carcinogenic effects of DMA(V) exposure in the rat is unclear. This uncertainty should be properly included into the risk assessment analysis for DMA(V) exposure in humans.

There were no follow up discussions of these statements.

## **2) Issue B. Modes of Carcinogenic Action for DMA<sup>V</sup> and Inorganic Arsenic**

### **B1) Mode of Action of DMA<sup>V</sup>:**

Member discussions mentioned the following: specific key events in the proposed mode of action; uncertainty in specific key events; cytotoxicity; whether damage is due to reactive oxygen species; the role of cell proliferation; if there was some possibility of genetic toxicity involved.

***Draft Consensus Remarks for B1. Mode of action of DMA<sup>V</sup>: Please 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.***

{Dr. Rossman for the Subgroup} The committee felt that there is adequate data to support an MOA for bladder carcinogenesis induced by high doses of DMA<sup>V</sup> in the rat that involves cytotoxicity to the bladder epithelium and increased, sustained regenerative proliferation as Key Events. The urine of DMA<sup>V</sup>-treated rats contains DMA<sup>III</sup> at levels that cause necrotic cytotoxicity in vitro, so it is reasonable to postulate that DMA<sup>III</sup> might mediate the necrotic cytotoxicity in the rat bladder. However, because the rat (but not the human) can produce TMAs<sup>III</sup> (and possibly other metabolites?) from DMA<sup>V</sup>, this compound cannot be excluded as a

mediator of the necrotic cytotoxicity. (Dr. Styblo: Also, comment on paper by Shen et al. about MMA<sup>III</sup> from DMA<sup>V</sup> exposure. Is this reasonable in light of the one-way metabolism?)

The committee felt that there is insufficient data to invoke ROS-induced DNA damage as a key event in the carcinogenic process, although that mechanism cannot be ruled out. Permanent genetic change is necessary for carcinogenesis, and it is unlikely that increased proliferation alone in the absence of increased genomic instability (increased mutation rate, aneuploidy, amplification, methylation changes, etc.) will result in the 3 or more changes needed to transform a normal cell to a tumor cell. Increased DNA damage could be induced by oxidants (perhaps related to DMA<sup>III</sup>- Dr. Styblo, please tie this together) but this has not been demonstrated in the bladder epithelium. Other sources of DNA damage exist. Inflammatory cells are one such source (although Dr. Cohen claimed very limited inflammation in the rat bladder, this needs further investigation). It is also possible that live cells exposed to the contents of necrotic cells may experience DNA damage (e.g. via “clastogenic factors”), but there is no evidence to support this mechanism either. (Drs. Klaunig and Barchowsky: Please comment on possible roles of oxidative or other signaling, keeping in mind that cells are already undergoing regenerative proliferation. Is there some way to get to genomic instability?)

The tumor response in the rat bladder system is non-linear, as is the key event (i.e. necrotic cytotoxicity). (Dr. Dragan: More on this please).

*Please 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.*

## **B2) Human Relevance of Animal DMAV MOA.**

Member discussions mentioned the following: levels of exposure rats vs. human; the similarity of the posed cascade of events from rats in humans; accumulation in humans; differences between rats and humans; how interspecies differences are incorporated into health assessments; PBPK differences; differences in the mouse vs. the rat; sequestration in the rat; adequacy of data to respond to the question; and a study in Chile showing no differences among younger and older population members in responding to arsenic exposure.

**Draft Consensus Remarks for B2: Human relevance of animal DMA<sup>V</sup> MOA:**  
***Please comment on the relevance of the postulated key events (see B1) to tumors in humans.***

{Dr. Rossman for the Subgroup} If high enough concentrations of DMA<sup>V</sup> were present in the human bladder, it is plausible that a similar response (necrosis followed by regenerative proliferation) would take place. No studies have been carried out on DMA<sup>V</sup>-induced bladder cancer in humans, so it is not known at this time whether there have been any cases. It would probably require very high concentrations that could result from an industrial accident or deliberate poisoning. Even in those cases, the exposure would probably have to be repeated long enough to give sustained high bladder levels.

Already mentioned is the fact that rats make TMAs<sup>III</sup> from DMA<sup>V</sup> and humans do not. Since TMAs<sup>III</sup> is even more toxic than DMA<sup>III</sup> (please provide reference Dr. Styblo), it is possible that the rat data over-estimates the human risk for bladder cancers from DMA<sup>V</sup>.

There is no data to suggest that the young are at greater or lesser risk with regard to DMA<sup>V</sup>-induced carcinogenesis.

*Please 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>.*

*Please comment on the Agency's conclusion that the young are likely to respond like the adult to the formation of bladder tumors following exposure to DMA.*

**B3) Modes of Carcinogenic Action from Exposure to Inorganic Arsenic**

Member discussions mentioned the following: lumping of endpoints and the possibility that cancers at different sites have different MOAs; the lack of data on the issue; reactive oxygen species; the possibility of essentiality; and human epidemiology data.

**Draft Consensus Remarks for B3. Modes of carcinogenic action from exposure to inorganic arsenic:** *Please comment on the conclusion that the available data support the hypothesis that multiple modes of action may be operational following exposure to inorganic arsenic.*

{Dr. Rossman for the Subgroup} The committee agrees that multiple modes of action may operate in carcinogenesis induced by inorganic arsenic. This is because there is simultaneous exposure to multiple metabolic products as well as multiple target organs. There are differences in metabolic capability in different organs, so that the composition of the metabolites can differ in different organs as well. Each

of the metabolites has its own cytotoxic and genotoxic capability. In general, the pentavalent compounds are less cytotoxic and genotoxic than are the trivalent compounds. (Dr. Brusick: Please go into more detail about specific compounds here, and I'll add something also about genomic instability).

Animal studies indicate that for some organs, transplacental carcinogenesis may occur (Dr. Waalkes: Please comment on properties of the mouse strain with regard to background rates. Also, comment on discrepancies between human and mouse tumor sites and possible reasons for discrepancies). Other studies indicate that for skin, arsenite acts as a cocarcinogen and not a complete carcinogen. This leaves open the possibility that a cocarcinogenic MOA may also operate for other organs, but this remains to be tested (only money is needed).

At his time one cannot dismiss the possibilities of hormesis effects in humans exposed to low-dose arsenic or the essentiality of arsenic to humans. These may explain some of the low-dose benefits seen in a variety of systems (Dr. Barchowsky: Please fill in here). If arsenic is essential for humans and/or if epidemiological data could be strengthened at the low-dose range to demonstrate either a low-dose benefit or no effect at low dose, then a threshold is certain. However, at this time, the data is lacking or problematic with regard to low-dose effects. This is an extremely important issue and should be investigated.

Follow up discussions of the statements for B1 through B3 focused on: high-linearity in animals of DMA<sup>V</sup>; complications to modeling from co-carcinogenicity; and lack of human evidence for DMA<sup>V</sup>.

The meeting was adjourned for the day and a start time for September 13, 2005's session was changed to begin at 7:30 a.m. to reflect the slippage of the day's agenda to accommodate a longer than planned public comment session.

## **Tuesday, September 13, 2005**

The meeting was reconvened at 7:30 a.m. Dr. Matanoski instructed the Panel Members to focus on the specific answers to the charge questions and the types of consensus statements that should be made so that we could finish the agenda on time.

### **3) Issue C. Selection of Data for Dose-Response Assessment**

#### **C1) Use of Animal Data for DMA<sup>V</sup>**

Member discussions mentioned the following: the possible use of human epidemiology data from inorganic arsenic studies in assessments for DMA<sup>V</sup>; uncertainty about the DMA species in rat urine; human measurement errors for DMA<sup>III</sup>; dose equivalency; methylation in humans; relative levels of DMA species in mouse urine after

inorganic arsenic dosing; whether rats are unique in their arsenic metabolism; site concordance in humans and rats; and dosimetry.

***Draft Consensus Remarks for C1. Use of animal data for DMA<sup>V</sup> : Please 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. Medinsky for the Subgroup} This question indirectly raises the issue as to the largest source of uncertainty for DMAV risk assessment—conventional interspecies extrapolation or extrapolation across various forms of As. The available material suggests that extrapolation across various forms of As would lead to the greatest degree of uncertainty in risk assessment.

The consensus of the panel is that the bladder tumor data from the DMAv rat bioassay is the most suitable data set for quantifying potential human cancer risk to DMAv. Given the complex metabolic fates of As and its various species, it is not advisable to use human data from iAs exposure to predict risk from DMAv. In this case, reliance on interspecies extrapolation using the rat bioassay data is the best alternative.

Although the panel agreed that the rat model is the preferred alternative, the document should discuss key uncertainties with using this work for human risk assessment. For example, rat bladder tumor data illustrating the mode of action for DMAV as a bladder carcinogen in rats seem quite convincing. Rats have been shown, however, to be highly sensitive to DMAV relative to the mouse (1,2). Methylation in the rat liver hepatocytes proceeds at a faster rate than in human hepatocytes; and rats have a considerably slower whole body clearance of DMA likely due to the fact that a significant portion of DMA is retained in the erythrocytes (3). The rat shows a 15 to 20 fold higher binding of arsenic to rat hemoglobin than to human hemoglobin (4). Human bladder tumors are primarily transitional cell carcinomas; rat bladder tumors are reported to bear some similarity pathologically to low-grade papillary tumors that occur in humans, but not to human invasive bladder tumors that display high grade malignancy (5). The foregoing, taken together, illustrates known substantial metabolic, pharmacokinetic and pharmacodynamic differences between rat and human. These differences should be discussed.

A second major uncertainty in the proposed use of bladder tumor data from rats is the unknown level of production of DMAIII in human bladder upon exposure to DMAV relative to rats. The few human exposure studies that exist seem to indicate little if any DMAIII production takes place given that DMAV is not absorbed well with approximately 80% of a dose of the parent compound being excreted in a short time after exposure (6,7).

Additionally rat urothelial cells are 3.5 times more sensitive to DMAIII than are human urothelial cells in in vitro studies (8). These toxicokinetic and toxicodynamic factors should be taken into account in the application of rat bladder tumor data to assess human bladder cancer risk. These factors will impact the choice of uncertainty factors since the weight of evidence indicates that rat is considerably more sensitive to bladder tumor induction from direct exposure to DMAV than are humans.

The urinary bladder tumors in rats occur as a very late event as, at least in the published report, it takes two or more years of continuous high dose exposure to DMAV in rats to induce these tumors. This equates to a human being who develops cancer after about 60-70 years of exposure. Are all urinary bladder cancer in arsenic exposed persons seen in people aged 65 or older? The other study (Gur et al.) was never published and cannot be critically evaluated yet great stock is placed in this study. The question is if this is such an important study why was it never published. These issues need discussion.

The documents are critical of the transplacental model for inorganic arsenic carcinogenesis because the work was done in a sensitive strain (C3H) with significant background of tumors in some tissues. It is an absolute fact that all cancers in all rodent and human tissues occur spontaneously, but implicit in this criticism is that if a tissue shows spontaneous tumors this negates any observations of chemical carcinogenesis in that tissue. If so all rodent carcinogenesis studies would be negated. This should be discussed.

Is there an absolute requirement for target site concordance between human and rodent studies in tumor target site required to make rodent studies valid? Similarly, are typically non- fatal cancers induced by arsenic (i.e. skin) given less weight in animal models or human exposures. General issues in rat urinary bladder cancer should be discussed, including non-specific induction at high concentrations of test substance in urine. There is evidence in many tissues that simple enhancement of proliferation is not associated with carcinogenesis.

***Please comment on whether the iAs epidemiology data can be used to inform the DMA<sup>V</sup> dose-response assessment derived from rat data with DMA<sup>V</sup>. If so, please discuss how such information might be used. (See Appendix).***

{Dr. Medinsky for the Subgroup} The panel consensus was that without more detailed information on target tissue dosimetry of As species human iAs epidemiology data would be of limited use to inform the DMAV dose-response assessment derived from rat data with DMAV. Direct exposure to iAs elicits a different cascade of metabolite concentrations with related differential kinetics compared to direct exposure to DMAV, therefore the iAs epidemiology data cannot reasonably be used to inform the DMAV

dose-response assessment derived from rat data with DMAV. In the absence of specific information on target tissue levels, assumptions would have to be made regarding the proportion of the iAs for human and DMAV for rodent that reaches the bladder tissue as the toxic DMA species.

In principle, epidemiology data from iAs exposed humans could be used to inform the DMA assessment to the extent that the data might be able to address the appropriateness of interspecies extrapolation, specifically the relative sensitivities of rat and human to bladder cancer following As exposure. However, as noted above in order to be useful some information on target tissue dose of DMA following human exposure to iAs and rodent exposure to DMAV would be necessary. With both tumor indices (human and rodent) expressed in terms of the same tissue dose rather than iAs or DMAV exposure levels, the relative sensitivities of the human and rodent could be assessed.

#### References

1. Rossman TG. (2003) *Mutat Res* 533:37-65.
2. Arnold LL et al. (2003) *Toxicol* 190:197-219.
3. Vahter M et al. (1984) *Archiv Environ Contam Toxicol* 13:259-264.
4. Lu M et al. (2004) *Chem Res Toxicol* 17:1733-42.
5. Cohen SM (2002b) *Toxicol Pathol* 30:663-671.
6. Buchet JP et al. (1981) *Int Arch Occupat Env Hlth* 48:71-79.
7. Marafante E et al. (1987) *J Appl Toxicol* 7:111-117.
8. Cohen et al.(2000a) *Chem Research Toxicol* 15:1150-1157.

There were no follow up discussions of these statements.

[NOTE: During the meeting, the discussion of question D1 followed C1 but for the sake of organization, these minutes will discuss C2 after C1.]

#### **C2) Use of Human Epidemiological Data from Direct iAs Exposure**

Member discussions mentioned the following: the continuing utility of the Taiwanese data set; the need for additional studies with requisite power; the relevance of the issue of power in the recent low dose arsenic studies; the utility of the previously discussed meta-analysis for elucidating a point of departure for arsenic; case-control study design implications; uncertainty in low dose studies; sources of error that can be associated with study data; the need for EPA to clarify how each study it considered prior to deciding on using the Taiwanese study compares to criteria which were important in deciding that the Taiwanese data remained the best for risk assessment; the need for EPA to better clarify the uncertainties in its analysis; the mobility of humans that are a part of epidemiology studies; lack of use of dose data in meta-analysis in favor of exposure surrogates; how the Bates study in Argentina compares to the Taiwanese outcomes; the impact of smoking in the Taiwanese study; the impact of exposure assessment in these studies; the need for low dose epidemiology studies in the U.S. that account for differences in the U.S. population relative to populations studied outside the U.S.; the need for continued evaluation of relevant characteristics in the Taiwanese study

populations relative to misclassification; the role of predisposing factors; whether the U.S. low dose studies confirm non-linearity; nutritional status affects on studies; co-carcinogenicity; and the need for more transparency in the EPA analysis.

**Draft Consensus Remarks for C2. Use of human epidemiological data from direct iAs exposure:** *Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans? Please discuss the rationale for your response*

*Do these data provide adequate characterization of the impact of childhood exposure to iAs? Please discuss the rationale for your response.*

[Dr. Cantor for the Subgroup] Yes. The Taiwanese dataset remains the most comprehensive data on population risk. It includes the largest study population, most complete characterization of arsenic levels in the wells, longest duration of follow-up and most complete case ascertainment, and includes consideration of risk across the lifespan.

Suggestion was made for sensitivity analyses, using highest level and lowest level exposures in the villages with more than one well to provide a range of the risk.

Other data sets from Chile, Argentina, and Taiwan should be used to scale the dose-response relationship at high exposures to inorganic arsenic. There are many datasets/ studies that EPA may not find useful for risk analysis (this includes the U.S. studies). These should be listed & described and their relative strengths and weaknesses presented.

Meta-analysis of various studies is suggested.

All of studies to be judged by same criteria to see what value of studies are relative to one another. Assumptions should be clearly laid out.

Teegarden: we should communicate uncertainties in the data and what should and should not be used. A table of strengths and weaknesses should be applied. Risk estimate should be produced with the assumptions used. Go through complete analysis using at least one other epidemiologic data set. Also, alternative approaches that could be used (???)

Matanoski: Caveats and epi problems & assumptions etc. and how you look at data should be apparent to anyone who uses the data. Needs this badly.

Teegarden: detailed assumptions and how variability and how they effect risk estimates should be included in the risk assessment bkgd doc't. .

There are inadequate data to characterize the impact of childhood exposure to inorganic arsenic with respect to carcinogenesis. That is, it is not clear whether children differ from adults with regard to their sensitivity to the carcinogenic effects of arsenic in drinking water.

Follow up discussions of these statements focused on: meta-analysis of the data; whether “actual risk” data existed and should be used in risk projections; consistency between Taiwanese study and Chilean study; need for transparency in EPA discussion of the analysis-compare the strengths and weaknesses of the various studies in tabular displays; and the need to clarify the inorganic arsenic document.

#### **4) Issue D. Approaches to Low-Dose Extrapolation for Inorganic Arsenic and DMA<sup>V</sup>**

##### **D1) Mode of Carcinogenic Action Understanding for DMA<sup>III</sup> and Implications for Dose Response Extrapolation to Estimate Human Cancer Risk**

Member discussions mentioned the following: nonlinearity of rat tumor response to DMA<sup>V</sup>; whether any step in a mode of action being nonlinear makes the complete MOA nonlinear; interpretation of low-dose epidemiology studies of inorganic arsenic; the lack of human data for DMA<sup>V</sup>; additivity of low doses with background arsenic levels; rat sensitivity to arsenic compared to humans; FQPA safety factor origins; partitioning of the uncertainty factor; kinetics of applied doses to target doses; rat vs. mouse similarities to human metabolism; pharmacodynamic data adequacy; and the relative uncertainty of a BMD<sub>10</sub> vs a BMD<sub>1</sub>.

##### **Draft Consensus Remarks for D1. Mode of carcinogenic action understanding for DMA<sup>V/III</sup> and implications for dose response extrapolation to estimate human cancer risk:**

*{Dr. Teeguarden for the Subgroup} Please comment on the scientific evidence and biological rationale in support of the nonlinear versus linear low dose extrapolation approaches,*

As a group we reached consensus that there was sufficient scientific support for the stated mode of action in rodents and that it was reasonable to assume that each of the key events represented in the mode of action could reasonably occur in humans. It was therefore the consensus opinion that the available data support the nonlinear approach for the risk assessment. The linear approach is not consistent with the data. As a point of clarification, while we generally expect that low doses of a compound may add to background processes and consequently some portion of the low dose region would have a linear slope (ignoring dynamics of course), these small incremental increases in the slope have no relationship to the slope of the dose response curve derived from the high dose animal toxicity data and can be ignored.

***(2)...which approach is more consistent with the available data on DMA<sup>V</sup> and current concepts of chemical carcinogenesis,***

See (1), above. We would support our conclusion, in general, by adopting the summary and analysis presented by OPP in their document, “Science Issue Paper: Mode of Carcinogenic Action for Cacodylic Acid and Recommendations for Dose Response Extrapolation.”

***(3)...how [should] scientific uncertainty should most appropriately be incorporated into low-dose extrapolation***

After some discussion, we viewed this question from the perspective of the EPA’s RfC guidelines proposed approach for interspecies uncertainty factors. That is, consider the differences between species to be the result of differences in pharmacokinetics and pharmacodynamics.

For the response of the bladder epithelium, cytotoxicity, probably the dose limiting key event in the mode of action, the consensus was that there is a case that could be made by the agency for pharmacodynamic equivalency between the test species, rats, and humans. In the context of the guidelines, this might be incorporated in the assessment as a reduction of the PD component of the factor of 10 uncertainty factor from 3 to one.

While it was the opinion that rats *might* deliver a higher dose of DMA<sup>III</sup> than humans to the bladder for a given dose of DMA<sup>V</sup>, the committee recognized that there was insufficient data on the comparative dosimetry from these species to make any conclusive statements about species differences in pharmacokinetics. There appears to be emerging data on DMA<sup>V</sup> kinetics which might be brought to bear on the question and the agency is encouraged to consider these data with respect to pharmacokinetic differences between the species.

The follow up discussion noted the need to mention deletion of the reactive oxygen species key event.

**D2) Implementation of the Recommendations of the NRC (2001):**

Member discussions mentioned the following: the continuing appropriateness of the NRC conclusion in the light of new studies; the impact of new low-dose studies; the context of the issue relative to the 2005 cancer guidelines; mode of action vs. epidemiologic data; the extent to which iAs MOA is understood; data needs that would have to be met to allow EPA to depart from linearity and whether such data currently exists; sensitivity analysis needs; genetic instability following multi-generational studies at low dose; the impact on risk assessment at low doses if one focuses on bladder cancer or lung cancer; MOA understanding at low dose; initiation and promotion; tumor generation aside from carcinogenicity at low doses; “J-shaped” curve possibilities for some endpoints; the fit of Taiwanese data to various curves; the effect of control groups

on point of departure selected; alternatives ways to look at risk; and variability of well water involved.

**Draft Consensus Remarks for D2. Implementation of the recommendations of the NRC (2001):** *Does the panel concur with the selection of a linear model following the recommendations of the NRC (2001) to estimate cancer risk at this time? Please discuss your response in light of the highly complex mode of action for iAs with its metabolites.*

{Dr. Hopenhayn for the Subgroup} The following points were considered in addressing this question:

- Absence of clear data on the different MOAs operating for each of the multiple target sites
- Lack of adequate human data at the lower range of iAs due to limitations in epidemiologic studies conducted to date
- Evidence from experimental studies using chronic, low doses of iAs (in the range of low human exposures from drinking water of 50 ug/L) demonstrates biologic effects that can lead or increase the development of tumors

Based on these points, the Panel agrees that a threshold for the effect of iAs in humans has not been demonstrated; there is no data to determine the shape of the dose response below a given point of departure and there is a linear response in the dose-range from the studies in Southwestern Taiwan. Therefore, at present we agree with the use of a linear model. Until more is learned about the complex properties and MOAs of iAs and its metabolites there is insufficient justification for the choice of a specific non-linear form of the dose-response relationship.

However, the Panel made several recommendations:

- a) Conduct a sensitivity analysis using both a linear and a quadratic terms for dose (Steve H. will correct/add to this)
- b) The use of different control groups should be considered, specifically: the overall population of Taiwan, the population of Southwestern Taiwan and the internal study sub-group in the lowest exposure range. The Panel suggests the use of internal controls as the most suitable.
- c) Given the problems mentioned with respect to the use of the median well water concentration in villages with more than one well measurement, it is suggested that the data be modeled and compared using the upper and lower ranges as well as the median

Comments from other Panel members to consider:

Dr. Rossman: This is not a standard genotoxic carcinogen and experiments at low doses may depend on other events. At a molecular level you could argue for a threshold but it is not applicable to humans  
Low doses= don't inhibit growth, sub-micromolar range;

Dr. Barchowsky: Biological effects seen in the the 50-100 ppb in the mice, increase in tumor growth.

Dr. Styblo: Trusts cell culture more than animals, because of the diet

### **D3) EPA Model Re-implementation:**

Member discussions mentioned the following: precision and accuracy of the re-implementation; inconsistent results between EPA implementation and “Morales” implementation for NRC; accessibility of the original code; errors in “R” implementation; how the model “works”; use of BIER IV; verification of population inputs to the model; and age-specific death rates.

**Draft Consensus Remarks for D3. EPA 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. *Please comment upon precision and accuracy of the re-implementation of the model.***

{Dr. Heeringa for the Subgroup} Implementation of model in EXCEL is commended. It serves as a check of implementation in alternative systems (e.g. R, S) and provides transparency for review by non-specialists. If the EPA returns to another model program, it should begin with original model formulas and not simply transcribe the EXCEL model. Use comparison of intermediate results from two model programs to debug and validate.

Model is a two-stage system with dose-response estimation in MCCancerFit.xls and Bier.xls for evaluation of LED(01) under the estimated dose response model.

Issues on Integrity of Program Inputs

a) MCCancerFit.xls – verify the person years of exposure data for the male and female controls. Female person years of exposure are less than that for males, a fact that is not consistent with general population structures and dynamics. EPA inputs agree with Morales, et al. (excluding age 85+) but the question of the gender balance in these data should be investigated. The model does not allocate a food input to the reference population. This is a decision that should be subjected to a sensitivity analysis. The food input parameter should be clearly documented.

b) Bier.xls – verify the 1996 Vital Statistics and U.S. Population inputs. The computed age specific mortality rates for men and women (e.g. men, age 20-24) do not match the rates published in Table 4 of Morales, et al.

c) Verify and document carefully all inputs for the SW Taiwan data, the reference population, U.S. 1996 population and vital statistics.

#### Integrity of Program Calculations

a) MCCancerFit.xls – for given data inputs, the empirical Bayes estimation appears to match the description.

b) Bier.xls – based on spreadsheet downloaded from Office of Water website, calculation of cancer specific survival (Row 13) appears to incorporate mortality through time I, not time I-1. This should be checked. Calculation of baseline survival appears to be correct. With this exception calculation of Excess Risk follows the Bier IV formula

c) Inclusion of 3-fold divisor to transform risk to U.S. population base (assuming exposure per kg is 3-fold higher) in SW Taiwanese population is not documented and should be a target for sensitivity studies. Since this is a parameter it should be so identified on the spreadsheet instead of hidden in calculations.

#### Theoretical extensions and uncertainty

a) Empirical Bayes for ER(x) as opposed to taking lower confidence limit for the dose response coefficient into the deterministic ER(x) computation.

b) Sensitivity/uncertainty

i) Carefully constructed and implemented Monte Carlo analysis of well concentrations for 22 villages with multiple wells. Still there are issues with how to allocate cases to wells within villages.

ii) MCCancerFit.xls- test sensitivity of the assumption that the reference population has 0 intake of arsenic via food.

iii) Multiplicative model for dose-response with quadratic dose term

iv) Age groupings as inputs. Test effect of 10-year or other groupings in both spreadsheets

v) Choice of reference population.

vi) Address the exposure/kg parameter. Treat as parameter input to Bier.xls not as a fixed constant in the calculation

c) Typos in Issue Paper

There were no follow up discussions of these statements.

**D4) Drinking Water Consumption Rates for SW Taiwanese Study Population:**

Member discussions mentioned the following: gender difference assumptions used; need for sensitivity analysis; the source of consumption values selected for the analysis; and gender differences in consumption patterns.

**Draft Consensus Remarks for D4. Available literature describing drinking water consumption rates for the southwestern Taiwanese study population: *What drinking water value does the panel recommend for use in deriving the cancer slope factor for inorganic arsenic?***

{Dr. Harlow for the Subgroup} The proposed drinking water values currently used by the EPA are generally perceived as adequate. The US water consumption data are obtained from a comprehensive US survey as compared to less comprehensive data bases for Taiwanese consumption. We note that relative to US consumption, overestimating water consumption in Taiwan decreases risk estimates and underestimating consumption increases risk estimates.

We recommend that

a) the EPA incorporate variability parameters for water consumption in their analysis for the Taiwanese population as they have done for the US population as per NRC recommendation;

b) given that assumptions about water consumption are an important source of variability in the risk estimates, that the EPA conduct sensitivity analyses of the impact of using a range of consumption values for the Taiwanese population.

Data on sex differences in consumption in Taiwan are limited, and a better justification for assuming different consumption levels by sex is needed, particularly given lack of sex difference in consumption in US and observed in studies from other countries.

The document should clarify how different sources of water intake are incorporated into the risk model including beverages other than water (e.g. green tea) and cooking water. Clarify both assumed consumption level and how introduced within the model.

There were no follow up discussions of these statements.

**D5) Selection of an Estimate of Dietary Intake of Arsenic from Food:**

Member discussions mentioned the following: need for sensitivity analysis; Taiwanese diet compared to Bangladesh and elsewhere; use of dietary information that fits the population being studied; arsenical use patterns in food crops; rice distribution patterns in Taiwan; cooking water; arsenic concentrations in foods; and seafood contributions to arsenic levels.

**Draft Consensus Remarks for D5. Selection of an estimate of dietary intake of arsenic from food: *What background dietary intake (of arsenic) value does the panel recommend for both the control population and study population of Southwestern Taiwan used in deriving the cancer slope factor for inorganic arsenic?***

{Dr. Yager for the Subgroup} Issue Paper: Inorganic Arsenic Cancer Slope Factor Table 4, p. 21 lists Summary Studies of Arsenic Consumption per day. EPA used a range of 30-50 µg per day arsenic intake from dry rice (uncooked) and dried yams in the diet of Southeastern Taiwan based on the work of Schoof et al., 1998 as listed in this table. Two members of the group agree on this approach.

Dr. Schoof, however, stated at the meeting that these data were obtained during the season when arsenic pesticides were not in use. Findings in the soil (5 ppm) indicated that arsenical pesticides had not been applied at this time even though it is known that arsenic was normally applied to soil (and taken up in food crops) during the wetter season. Therefore, Dr. Schoof made the statement that her data likely substantially underestimate the dietary arsenic intake from food in this population. Based on this information, and the data presented in Table 4, it is also recommended that a range of values from 30 µg/day up to perhaps 250 µg/day be run in a sensitivity analysis to assess the impact of this range of dietary intakes on risk of lung and bladder cancer from exposure via drinking water.

The sensitivity analysis of the impact of dietary arsenic uptake using a range of data from high arsenic-exposed populations rather than just the one data point from Schoof et al. is unlikely to introduce larger uncertainty than the myriad dietary differences – protein deficiency, Se, Zn, folate deficiency etc. –between this population and the US population.

The intake of iAs in seafood/fish needs to be considered.

The source of data for intake from other beverages and cooking water needs to be more fully discussed; the strength of the data assessed, and included in a sensitivity analysis to see what the impact is on estimated cancer risk.

Issue of control group—Choice of control population should also include the known value for arsenic exposure via food intake in the control population and/or data sources or assumptions and the relative strength of those assumptions regarding comparability of the control populations, if control populations are employed in the analysis.

Data-based or supported assumptions on the comparability of control group in terms of intake from iAs in food, other beverages, such as green tea, and cooking water with drinking water exposed population and impact of those factors on a range of risk

Stated arsenic concentrations in food are somewhat dependent upon differential extraction processes and different analytical procedures used in different laboratories on different food stuffs.

Laboratory extraction procedures are not usually designed, however, to equate with that portion of arsenic in food that may be bioavailable. This is an area for research.

Does it change the slope if you weight the model with weighting on change of iAs level? What is the impact of differences in iAs background (from dietary sources) for each village?

Follow up discussions of these statements focused on: the 250 µg/day value and a need to caveat section with a statement on analytical limitations in the studies.

## **G. Action Items**

Members agreed on the next steps to take. These include:

- a) DFO will send the compiled “draft consensus remarks” to all Panelists by September 14;
- b) each Charge Subgroup will flesh out its “draft consensus remarks” into a report section draft by October 14, 2005;
- c) Chair/DFO will compile all sections into a draft report and circulate it to the Panel by November 1;
- d) Panelists will comment on the draft report by November 15;

e) We will hold a Panel conference call to approve the draft document on or about November 30;

f) deliver the final Panel Draft Report to the Board during the first week of December 2005.

The DFO reminded the Members that during the writing phase of their report to the Administrator that they should not have interactions with Agency representatives or the public on the report. Such interactions could make a final report vulnerable to charges of outside influence. Any information flow between panelists as they write in their Subgroups should be copied to the DFO so they become a part of the public record. Also, any member of the public or agency needing to provide information to the Panel must do so through the DFO.

The Agency representatives thanked the Panel Members for their assistance and the meeting was adjourned by the DFO at 3:00 p.m.

Respectfully Submitted:

**/ Signed /**

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Thomas O. Miller  
Designated Federal Officer

Certified as True:

**/ Signed /**

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Dr. Genevieve Matanoski  
Chair, EPA Science Advisory Board  
Arsenic Review Panel

## **ATTACHMENTS (Available in hard copy)**

Attachment A:	Panel Roster
Attachment B:	FR Announcement of Meeting (70FR43144, July 26, 2005)
Attachment C:	Sign in sheets
Attachment D:	Agenda for the Meeting
Attachment E:	Agency Presentation: Dr. Wood
Attachment F1:	Agency Presentation: Dr. Dellarco
Attachment F2:	Agency Presentation: Dr. Lowit
Attachment F3:	Agency Response from Dr. Nesnow
Attachment G:	Agency Presentation: Dr. Doyle and Dr. Chen
Attachment H:	Agency Presentation: Dr. Farland
Attachment I:	Public Comment List 1 and Revised List
Attachment J:	Public Comment: Dr. Kayajanian
Attachment K:	Public Comment: Dr. Schoof
Attachment L:	Public Comment: Dr. DeSesso
Attachment M:	Public Comment: Dr. Brown
Attachment N:	Public Comment: Dr. Lamm
Attachment O:	Public Comment: Dr. Mink
Attachment P:	Public Comment: Dr. Tsuji
Attachment Q:	Public Comment: Dr. Cohen
Attachment R:	Public Comment: Dr. Gordon
Attachment S:	Public Comment: Dr. Beck
Attachment T:	Public Comment: Dr. Beck for Dr. Armbruster
Attachment U:	Public Comment: Dr. Sass
Attachment V:	Charge to the EPA SAB Arsenic Review Panel 7/25/05
Attachment W:	Science Issue Paper: Mode of Carcinogenic Action for DMA
Attachment X:	Toxicological Review of Ingested Inorganic Arsenic
Attachment Y:	Issue Paper: Inorganic Arsenic Cancer Slope Factor 7/23/05
Attachment Z:	Compilation of Premeeting Comments
Attachment AA:	Panelist Presentation by Dr. X. Chris Le