

Comment 4: Remove the Le, 2000 citation at his request – does not show “major” urinary metabolite (page 13, paragraph 1).

Comment 5: How does the ARP want to handle Dr. Rosen’s “absence of evidence” issue in regard to item 2 (page 13)

Comment 6: Does the ARP accept Dr. Teeguarden’s request to expand the PBPK benefit to helping us understand MOA, not just dosimetry? (page 15).

Section 3.2.2 Response to Mixtures of Metabolites: Tumor profiles vary with arsenicals administered. There are larger mixtures of metabolites after iAs exposure than after DMAV exposure. ***Charge Question A2: Comment on the use, in DMAV assessment, of data derived from rodent exposures to organic arsenicals vs. data derived from direct iAs human exposure.***

Comment 7: Many from ARP noted the need to revise the language in paragraph 1 of A2 to avoid the statement “...this panel has no choice, but to recommend...”Dr. Matanoski and Dr. Teeguarden suggested alternatives. (page 16)

Section 3.3.1 Mode of Action of DMA^V: Two common assumptions in EPA cancer risk assessments concern the notions that data on animal tumors are predictive of human cancer and animal tumor effects in high dose studies predict human risk at lower environmental exposures. MOA information informs these assumptions. MOA data are available for DMAV and were used in EPA’s evaluation. ***Charge Question B1: Comment on sufficiency of evidence to establish the animal MOA for DMAV. Are the EPA conclusions sound? Comment on whether the key events in DMA^V MOA are supported by evidence.***

Comment 8: Dr. Teeguarden points out the importance of ROS to how risk assessment is conducted. He calls for stating our criteria for sufficient evidence and to outline the MOA in more detail than now (e.g., as done in D1) and to make sure that B1 and D1 agree. He also notes that if the authors do not believe that increased cell proliferation is not enough for carcinogenesis that they argue for a different process that is likely low dose linear. How is this to be handled? (page 18).

Comment 9: Dr. Teeguarden notes that the discussion in this section is as speculative as the ROS suggestion. Replacing one speculation with another is not satisfying. Plausible alternative pathways are not an argument against a stated MOA. Articulate why data are not sufficient to support ROS – don’t just suggest possible alternatives (page 18-19). Build on D1 argument?

Section 3.3.2. There is little to no data suggesting that with sufficient DMAIII present, that key precursor events and tumor formation would not occur in humans exposed to DMAV. ***Charge Question B2. Human Relevance of DMAV MOA: Comment on the***

postulated key events to human tumor production. How could differences between human populations and experimental animals be accounted for in the DMA risk assessment?

Comment 10: Dr. Rossman notes that TMA discussion in paragraph 2 is confusing. (page 20-21).

Comment 11: Paragraphs 2 and 3 need clarification regarding whether there are no data because there are no tests or whether tests have been done but their results are not clear. The paragraphs might be combined and expanded to say more. Cite data if it exists.

Section 3.3.3. Modes of carcinogenic action from exposure to inorganic arsenic:

Inorganic arsenic undergoes successive methylation steps in humans to produce intermediate arsenical products each with its own toxicity. ***Charge Question B3: Comment on the conclusion that available data support multiple MOAs after iAs exposure?***

Comment 12: Dr. Matanoski asks for clarification of which compounds are genotoxic and which are not – the statement is not clear as now written. Which ones referred to have no data? (p 22).

Comment 13: Dr. Hopenhayn asks if micronuclei observed in epi studies indicate genotoxicity. Dr. Rossman responded to the question. How much of the response should be added to the section? Also, what is the bottom line of the response? (p 22-23).

Comment 14: The discussion on essentiality is not clear and Dr. Rosen does not agree with the premise. He offers a possible explanation to counter the Uthus citation. What does the ARP want to say here? (p 24).

Comment 15: Should Dr. Brusick’s suggestion for more research be added?

Section 3.4.1 Use of animal data for DMA^V: A number of different types of rodent studies exist for DMA^V. ***Charge Question C1: Is the rat bioassay data showing bladder tumors the most suitable for DMA^V risk estimation?***

Comment 16: Dr. Le suggests referring to section 3.2.1 in paragraph 2 of this section of C1 (p 25). The language in C1 may also help clarify the similar discussion in A2 (p 16).

Comment 17: Dr. Waalkes says 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. (p 26)

Comment 18: Dr. Styblo suggests rewording the statement on DMA^{III} production after DMA^V exposure. There are no studies on this rather they are on DMA^{III} production after iAs exposure. (p 26) See A1 also.

Comment 19: Dr. Styblo suggests 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^V exposure (p 27).

Comment 20: Also see comment 32 on page 41. The statement regarding the FQPA Safety Factor reduction needs to be clear that it applies to DMA's pesticidal 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)

Comment 21: Dr. Matanoski asks 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)

Comment 22: Dr. Rossman asks for clarification of the terms “non-specific induction of tumors” (p 28).

Comment 23: Dr. Rossman suggests adding information on co-carcinogenesis to the discussion on C3H mouse carcinogenicity. Is there an embedded policy issue here? (p 28)

Charge Question C1 – Part 2: Comment on whether inorganic arsenic epi-data can inform DMA dose-response assessments that are based on rat data on DMA exposure.

No Comments raised.

Section 3.4.2 Additional US epi-studies have been conducted on inorganic arsenic in drinking water since the NRC 2001 report. ***Charge Question C2: Does the SAB agree that the Taiwanese data set is still the most appropriate for estimating human cancer risk?***

Comment 24: Dr. Matanoski points out a “village number” difference (21 vs. 22) between page 30 and 31. She notes that many past analyses and peer reviews have been conducted on the Taiwanese data set and suggests this may support their strength. She points out the need to clarify the “reliability of exposure” statement and its relation to precision. (p 30).

Comment 25: Dr. Teeguarden suggests a different wording to the ending of paragraph 2 in C2 to say that Taiwanese data is not enough for human risk assessment and that additional work is needed. Even though the dataset still seems to be the most appropriate. (p 30). He also asks for a more specific statement in place of the “be considered by EPA” statement now in the discussion (p 30).

Comment 26: Dr. Teeguarden asks for stronger language than “it should be possible” relative to the need to look at other data sets for risk assessment (p 31)

Comment 27: Dr. Yager suggests a lengthy insertion on “integrative analysis.” She also responds to Dr. Harlow’s comments on the issue. (p 32-34) Drs. Matanoski and Hopenhayn also comment on the lack of clarity in the current section. (p 35) **DFO NOTE: I THINK THIS IS WHERE THIS FITS---** Also, Dr. Harlow’s retransmission of her suggestions for this section are in the compilation of member comments on the second draft of the report.

Charge Question C2 – Part 2: Do the data provide adequate characterization of the impact of childhood exposure to inorganic arsenic?

Comment 28: Dr. Hopenhayn rewords the last paragraph in the C2 discussion.

Section 3.5.1 Mode of Carcinogenic Action Understanding for DMAV and

Implications for Dose-Response: The 2005 cancer guidelines focus on MOA and prefer a biologically based model for estimating risk. There is not sufficient data on DMAV to do this. ***Charge Question D1: Comment on the evidence and biological rationale for nonlinear versus linear low dose extrapolation approaches for DMAV. How should uncertainty be handled?***

Comment 29: The discussion of MOA (p 36-38) needs several clarifications and the ROS issue seems to have inconsistencies within the section and possibly with ROS discussion in Question B1 (p 17-18).

Comment 30: A number of comments are embedded in the genotoxicity section (p 38-39) and Dr. Teeguarden suggests that the final paragraph on 39 be incorporated into B3.

Charge Question D1; Part 2: which approach is more consistent with available DMAV data...

No comments embedded

Charge Question D1; Part 3 How should uncertainty be handled?

Comment 31: Dr. Medinsky notes the need to consistently use pharmaco- or toxico- prefixes in the discussions. Also a similar need exists for the terms “uncertainty factors” vs. “safety factors.” (p 40)

Comment 32: This is the same issue as raised in comment 20 on charge question C1. Here it has more dimension and Dr. Medinsky suggests it also needs to be reconciled among this charge question, question C1 and also questions A1 and A2. The need also exists to ensure that when the safety factor issue is discussed ARP clearly ties the discussion to DMA as that is the pesticide-FQPA link that is the point of the question. The policy dimension needs to be clear as well. (p. 41).

Section 3.5.2. Implementation of the Recommendations of the NRC 2001: EPA 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: Does the panel concur with selection of the linear model for iAs cancer risk at this time?***

No Comments made.

Section 3.5.3 EPA Model Reimplementation: EPA reimplemented the NRC 2001 model in language R and in an Excel spreadsheet. They conducted extensive testing of the resulting code. ***Charge Question D3: Comment on the precision and accuracy of the re-implementation.***

Comment 33: 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).(p. 46-47).

Section 3.5.4. Available literature describing drinking water consumption rates for the southwestern Taiwanese study population: 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: What drinking water value does the panel recommend to use in deriving the cancer slope factor for iAs?***

Comment 34: Dr. Harlow asks if ARP should recommend analyses based on the extremes of the range.

Section 3.5.5 Selection of an Estimate of Dietary Intake of Arsenic from Food: NRC found that the ED01’s sensitivity to changes in food intake from 50 to 30 micrograms perday changed the ED01 only about 1%. New studies exist

and EPA currently models dietary intake for several levels. **Charge Question D5:** *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?*

Comment 35: There are several embedded suggested changes to the statements in this section. What is the resolution?

Attachment 1

Schema of iAs Metabolism in the Rat and Human

Rat

Human

