

interpretation. I suggest that the responses to B1 and D1 are modified to state that the Panel did not reach agreement on this matter. I do not think we need to provide a detailed review and evaluation of experimental data for or against this mechanism as suggested by JT. BTW, there was a chance to discuss this apparent disagreement earlier in the process. As far as I remember, there were no major objections to the current interpretation at the meeting or when the first draft was under preparation. The detailed comments on MOA should be provided only in the response to B1. D1 should deal specifically with dose response issues, referring to B1 for details on MOA.

3. I have several specific corrections/suggestions. These are as follows:

- a) P.12, line 32, should read “...and in some species to trimethyl-As (TMA) metabolites...” TMA is a general abbreviation for trimethyl-As species that does not specify the oxidation state of As in a compound, while TMAVO and TMAIII are specific abbreviations for pentavalent trimethylarsine oxide and trivalent trimethylarsine, respectively.
- b) P.14, line 27-28, should in my opinion read “...specific nutrients (e.g., selenium) or malnutrition. Poor nutrition has been shown to induce expression of”
- c) I would ask Dr. Medinsky if she can/want to modify the PBPK part of the response to A1 (p.14) to reflect JT’s comments. Let’s keep in mind that the response to A1 is supposed to comment on metabolic differences between rats and humans. Any other related comments should be brief and well-pointed.
- d) P.18, lines 2 and 3: omit trimethylarsine oxide and trimethylarsine. Use only the respective abbreviations that were defined earlier in the text.
- e) I stand behind my previous comments regarding the data (or lack of it) on the metabolism of DMA(V/III) in humans (p.26, lines 40-42) and p.27, lines 11-14. Changes should be made with consensus of the other panel members.
- f) P.37, lines 3,4: the sentence “A role for other rat DMAV metabolites, trimethylarsine oxide (TMAVne (TMAsIII) (Waters, et al., 2004) cannot be excluded as contributors of the necrotic cytotoxicity in rats exposed to DMAV.” should be changed to: “Other rat DMAV metabolites, TMAVO or TMAsIII (Waters, et al., 2004) cannot be excluded as contributors of the necrotic cytotoxicity in rats exposed to DMAV.” Again, there is no need to spell out the names of these arsenicals.
- g) P.41, line 16,17: MM is right. I also disagree with this statement. We do not know how much DMA(III) can be produced by humans exposed to DMA(V). It would be a mistake to imply that rats can produce more DMA(III) than humans. The first part of this sentence should be omitted. The sentence should start with :”The committee recognized...”

That's all I can do at this time. I am afraid the rest must be done during the meeting. I think the document reads quite well as it is, although the insertions of members' comments into the text make it difficult to get the whole picture. Clearly, there is still a lot of work left for the January meeting.

I am forwarding this e-mail to the other members of my subpanel and to Toby Rossman for comments. Let me know if you have questions and have a Happy and Successful New Year!

Mirek

2. Dr. Sioban Harlow

A. 11/21/05

Comments on Nov. 10 Draft

(Insert paragraphs below in C2 following paragraph 6, p. 25, line 13)

As recommended in the preceding sections, aggregate results, particularly on bladder cancer risk, from multiple published epidemiology studies of low level arsenic-exposed populations could be considered in a more formal secondary integrative analysis and compared with the main analysis for concordance. (REPETITIVE OF WHAT IS ALREADY STATED)A sensitivity analysis to formally evaluate the potential impact of sources of bias (non-random error) in the low level case control and cohort studies is recommended since non-differential misclassification cannot be routinely assumed.

PERHAPS THIS COULD BE THE START OF PARAGRAPH 2 PAGE 24 (then the important caveats would follow) Several recent arsenic epidemiology studies have the advantage of data with exposure assessment at a range of exposure levels relevant to those experienced by the US population—exposure levels in these studies range from 0.5 to 160 µg/L inorganic arsenic in drinking water (Bates et al., 1995; Karagas et al., 2004; Lewis et al., 1999; Kurttio et al., 1999; Steinmaus et al., 2003; Bates et al., 2004). Most of these populations have a nutritional and genetic background similar to that of U.S. or were conducted in a U.S. population.

THESE NEXT PARAGRAPHS LEAD TO A RECOMMENDATION THAT EPA FURTHER DEVELOP ITS CURRENT RISK ASSESSMENT METHODOLOGY TO CONSIDER THE APPLICABILITY OF RECENT STATISTICAL DEVELOPMENTS FOR ANALYZING DATA FROM SEVERAL STUDIES SIMULTANEOUSLY. THIS IS OBVIOUSLY DESIRABLE. HOWEVER, THE CORRECT APPROACH IS NOT SELF-EVIDENT AND WE HAVE NOT CONDUCTED A FORMAL EVALUATION WHETHER OR HOW THIS WOULD BE BEST ACHIEVED. THE TERM “RISK ASSESSMENT” IS USED TO DENOTE MUTIPLE SPECIFIC CONCEPTS NOT ALL OF WHICH ARE COMPARABLE TO THE FORMAL EPA PROCESS. IN THIS VERSION THE TERM “INTEGRATIVE ANALYSIS” IS USED, WHICH IS LIKELY BETTER THAN THE PRIOR TERM”META-ANALYSIS” (WHICH HAS SPECIFIC MEANINGS IN A CONTEXT QUITE DIFFERENT THAN EPA RISK ASSESSMENT) BUT DOES NOT REFER TO A SPECIFIC METHODOLOGY. IT IS LIKELY APPROPRIATE TO USE THE PLATFORM OF THIS REPORT TO ENCOURAGE EPA TO EVALUATE HOW BEST TO INCORPORATE THESE NEW ADVANCES IN THEIR RISK ASSESSMENT METHODOLOGY BUT I THINK THAT RECOMMENDATION SHOULD BE SHORT, SUCCINCT AND CLEARLY

STATE THAT WE CANNOT AT THIS POINT RECOMMEND A SPECIFIC METHODOLOGICAL APPROACH

Precedents for formally integrating health outcome information from a number of epidemiology studies exist. Although, ideally, one would prefer individual measures of exposure to be available in all studies, it is recognized that the Taiwan study of 42 villages herein recommended as the basis for arsenic cancer risk estimation is an ecological study with uncertainty as to individual exposure levels. Recommendations for assessing the range of uncertainty have been put forth in this report in the section immediately following.

Arsenic epidemiological literature is an instance in which a number of quality (but not ideal) epidemiology studies are available. Quantitative exposure-response modeling have been conducted and health risks estimated for methylmercury with an integrated risk analysis carried out utilizing multiple epidemiology studies (NRC/NAS,2000; Konig et al., 2005; Bouzan et al., 2005; Cohen et al., 2005a; Cohen et al., 2005b) REFERENCES ARE IMPORTANT BUT DETAIL IS EXTRANEIOUS TO THIS REPORTTHIS POINT IS ALREADY MADE ON PAGE 25 line 4-13

For most compounds of human health concern, epidemiologic data are generally not available (see A2); but occasionally, as in the case of arsenic, one or perhaps a few epidemiology studies will be available. To improve validity, it is important to support human cancer risk estimates using the maximum available scientific information and contemporary risk assessment methodology. EPA's current cancer risk assessment methodology relies on choosing a single epidemiological study to derive a cancer slope factor that is then used to extrapolate health effects considerably below the exposure levels observed in that study. There are a number of arsenic epidemiology studies now available; there are published methods for quantitatively integrating results from multiple studies (Coull et al., 2003; Ryan, 2005).

Although the "low" arsenic exposure epidemiology studies cannot by themselves provide a basis for dose-response modeling because of lack of data at the higher exposure levels (see D2), they do provide some data on the relative risks of bladder cancer for humans exposed at low levels. The Panel suggests, as described in detail in this section that an effort be made to conduct a secondary integrative analysis applying similar approaches to those described above to assess concordance with exposure-response models derived from the outcome of the primary analysis.

References

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NRC/NAS (2000) Toxicological Effects of Methylmercury. National Research Council, National Academy of Sciences, National Academy Press, Washington, DC.

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Coull BA, Mezzetti M, Ryan L (2003) A Bayesian hierarchical model for risk assessment of methylmercury. *J Agric Biol Environ Stat* 8(3):253-270.

Ryan LM (2005) Effects of prenatal methylmercury on childhood IQ: a synthesis of three studies. Report to the US Environmental Protection Agency.

B. Harlow, 1-08-2006:

Tom -- I have recent my comments on the JY insertion which did not appear in the reline document seperately.

In general I concur with many of the stated concerns (often from JT) about being more circumscribed in our response. I often find the digressions distracting regarding the actual request from EPA (it becomes hard to see our clear recommendation) and the lack of consistency on several points across the document is problematic. SO overall, I would agree with the need to focus our responses, reduce tangential digressions and clarify recommendations, which is my specific concern with the Yager insertion.

A few specific points.

Page ii Line 34 Siobán not Sioban (I like to get the dot in over the b too but newer word doesnt have the correct script)

Page 26 line 13-20. I concur with BR, that we should be careful in claiming essentiality. Hormesis can occur without claiming essentiality.

Page 32 lines 25-29 JT's comments. Strike “, but given its liminations ... risks to humans”. “... and compare risk estimates made using this data are warranted as suggested in the following sections.”

Page 32, line 41. A second risk analysis could be conducted using the Chilean data, to the extent possible given availability of the Chilean data.

Page 34-36 JY's insertion; and comments responding to my questions. No where are my comments or suggested edits of JY's insertion provided. What happened to those. Should my comments not at least appear as well as my suggested edit of her insertion?

Page 52 – in D4, we are asked to recommend a water consumption level - -I realize we have not done that so perhaps we are in fact non responsive on this point.

3. Dr. Dr. Steve Heeringa:

A. 01/16/2006 Email Note:

Good morning Tom,

I have reviewed the "mark up" draft of the Arsenic Panel report that you prepared on 12/27/2005. I have a number of typographical, word use edits that I could pass along but they are minor and I would prefer to wait until we see a consensus draft that follows our Panel's discussion on 01/24.

I have attached an MS Word document that contains MathType V equations with a small subscript change in the hazard model expressions that appear in 3.5.2 and 3.5.3 (change "C" to "dose" in hazard subscript). These can be cut and pasted into the next draft revision. It is a small change but standardizes the subscripts used on the left- and right-hand sides of the equations.

I have also noted Dr. Matanoski's and Harlow's comments regarding my draft comments (page 46) on the need to check the demographic data inputs for the computation of the Southwest Taiwan cancer hazard rates. I queried my Michigan colleagues (Arland Thornton, Li_Shou Yang) who have experience with demographic and family research in Taiwan and they have only one hypotheses regarding the surplus of males to females in the ages 20-55 over the reference period 1973-1986.

Dr. Yang provided this response:

"You can find a life table in Taiwan-Fukien Demographic Fact Book published between 1970 and 1985. After 1985, Demographic Fact Book no longer provides life table. Heath Statistics (published by Department of Health, Executive Yuan, ROC) is another source where you can found the causes of death and raw data for life table. The 1989 Heath Statistics (p. 58) published a table for life expectancy of Taiwan Area, 1950-89. Unfortunately, the life table has not been included in Health Statistics until 1990.

The surplus of male to female you found among some adult age groups during 1970-90 is due to the migration to Taiwan around 1949 when the Communist Party took over the Mainland China. Many young men of ages 15-29 serving in the military moved to Taiwan at that time. They contribute to the surplus of male to female of certain age groups in the subsequent years."

I have not yet looked at the life table sources that Dr. Yang cites. Since the persons years of exposure data used in the Morales et al. and other analyses begins in 1973, an 18 year old male who arrived in 1949 would be 43 years old in 1973. It could be that younger male children were also brought to Taiwan at higher rates during the period following the Communist take over. I am sure that there is a complex set of factors that influence the male:female ratios observed in Taiwan. I would be happy to downplay our guidance to EPA on this issue but I would not want to lose track of it entirely. I will try to locate and review the original sources cited by Morales and Chen before we meet.

Best wishes,

Attachment:

EPA SAB Arsenic Review Panel

Formula Edits from S. Heeringa (Created in MathType V)—formulae may be cut and pasted

Pages reference are to 12/27/2005 “Mark-up” document prepared by Tom Miller.

Page 43 edit:

$$\lambda_{i,dose} = \exp(a_1 + a_2 \cdot age_i + a_3 \cdot age_i^2) \cdot \exp(\beta_0 + \beta_1 \cdot dose + \beta_2 \cdot dose^2)$$

Page 45 edit:

$$\lambda_{i,dose} = \exp(a_1 + a_2 \cdot age_i + a_3 \cdot age_i^2) \cdot (1 + \beta \cdot dose)$$

Page 48 edit:

$$\lambda_{i,dose} = \exp(a_1 + a_2 \cdot age_i + a_3 \cdot age_i^2) \cdot \exp(\beta_0 + \beta_1 \cdot dose + \beta_2 \cdot dose^2)$$

B. Heeringa, 1-18-2006 Email:

I have investigated the issue of the Taiwanese demographic structure (male surplus in young and middle age adulthood) using original sources (Health Statistics for Taiwan). I have also returned to Wu, et al.(1989), Chen, et al. (1992) and Morales et al. (2000) to establish consistency in tabulated data for exposure years for these three papers. I have come to several conclusions that I will put forward at our meeting:

- 1) The "male surplus" in the person years of exposure data for the

reference populations in the SW Taiwan region and for the nation accurately reflect the official statistics. Therefore, I will recommend that we drop the statement that these data reflect a departure from normal demographic expectations. That statement is clearly prejudiced by my US/developed world view and is not needed.

2) A comparison of the tabulated "person years of exposure" data for the 42 village population shows minor discrepancies across sources (generally within 2-3%) in the reported values for gender, age category and exposure category cells. Interestingly, the Wu and Chen papers have the same control totals for all men and all women but the values for a category such as men, age 20-29 with <.30 ppm differ. I will try to present a few examples and also verify that the Cancerfit models have the correct entries (ala Morales). In short, we may still want to recommend a review of the person year exposure inputs to establish a definitive original source and verify that the inputs match the cited source.

4. Dr. Matanoski, 1-18-2006

Critique of SAB Arsenic Panel combined report from 12/20/2005

Page 12 I think we need to consider how best to approach the problem of microbials and As. If they did not want to consider the effect of microbials on the DMAV we don't need to write a long discussion of the effects of agents on the fate of DMAV. It might be helpful to simply recognize that they will be writing on this topic and to warn them that we had recognized two points of interest in this issue, the general environmental changes that can take place in the pesticide due to environmental microbes and the intestinal changes that might take place in the body depending on the microbes from a specific species. The latter consideration might be important for the current evaluation of the outcomes of the ingestion of the pesticide.

Page 13. Since both Le and Valenzuela have shown DMAIII to be a metabolite from iAs, it would seem to be appropriate to simply remove the word "major" since it is a relative term and continue with the rest of the discussion.

Page 14. Discussion of intestinal microorganisms here is very good.

Page 19. JT is certainly correct. It is not appropriate for us to speculate on other modes of action unless we can justify our speculations as being more relevant than those of EPA. To make them more relevant, it would also be helpful to relate these MOAs to humans. That is the speculation should extend to whether alternative MOA is more likely in humans and therefore more relevant. Can we do that for any of the proposed MOAs?

Page 20. In discussing human relevance of dose it may be important to consider the fact that the human has differences in urinary function that may play a role in dose to bladder. The human deliberately retains urine often for long periods. This is especially true in older men. The location of the bladder cancers in humans tend to be very localized in a limited area of the bladder where there is a high rate of cell turnover. Would these factors play a role in making their responses different from those of rats? Humans may also have several toxic agents in the bladder at one time that may induce cytotoxicity in addition to or in interaction with the DMAV.

Page 22. Since you mention micronuclei for both rat and mouse, it is not clear to me why you have rejected the human data. You need to clarify this further to make the argument .

Page 23. As part of the discussion about micronuclei, I am confused by the statement about Giri's studies. The presence of MN in all three organ systems does not require that all systems necessarily have cancers especially when one system represents a soft tissue cancer and the others do not. Dose and other factors may play a role. Haven't some of the exposure to inorganic As also had non-Hodgkins lymphomas as an outcome? I need to check this.

Page 24. The section on hormesis is very confusing. Are you trying to tell me that As is essential in the steps of vascularization or that As alters that process? If As alters vascularization, then I have a hard time saying that it is essential since many diseases could occur because of abnormal vascularization, for example malformations. It might even promote growth \. It sounds like the same argument for radiation. For example radiation promotes growth in plants at least but leaves them stunted and fruitless possibly because of too rapid growth.

Page 26. I agree that reliance on the grade of bladder tumors in mice and humans as an argument against similarity of the cancers is not a good one. We believe that the tumors in humans can be a progression from benign or in situ lesions into invasive cancer. As pointed out the sacrificing of the animals deliberately identifies the cancers only in the early stages as we would in screening humans.

Page 27. MS has made an important point. The report does not offer any direct evidence that rats are more sensitive to bladder cancer than humans because there is no data in humans. This has been a common problem where a lack of data is equated with no effect. We should check for this throughout. We can say it is inferred based on available metabolic data if that is adequate for both rats and humans.

The question then is whether that is the basis for your conclusion about the safety factor. In addition, we must be absolutely clear what safety factor we are talking about.

Lines 24-31. The points made by JT and MM are very important. Suggesting we reduce the safety factor already steps into policy arena. To suggest a level means we should have strong scientific reasons why that level and not any other should be selected. Barring that kind of consideration , a suggestion that the level should be reduced may fit scientifically.

Again age of onset of rat tumors compared to humans is dangerous as is the suggestion that there are differences in tumor stage. Sacrificing of the animals tends to fix the age of the tumor onset. In addition, this is a tumor in humans occurs with peak in eighties. The age of onset is slightly younger in cancers related to dye exposures. Because of this advanced age it is surmised that this cancer has a very long latency period estimated by some to be over 30 years.

Page 28. lines 32-39 Although I have heard the argument many times about the use of a sensitive species, I can suggest a counter argument. There are believed to be individuals who are more sensitive to some cancers and bladder is one because of their enzymatic makeup or other reasons related to genetics or possibly other exposures. Therefore, the sensitive animal species may reflect the sensitive human species. There may indeed be some kind of cocarcinogenesis in both species. In human testing of risk from an exposure in a population with an existing high risk of the disease, while it increases the number of outcomes, may also decrease the ability to determine the true results from the exposure because of background noise. Is that not a consideration in animals?

Another point in the statement is whether we are going to critique errors in the document in that section. If so, we must be careful in our conclusions. Paps can diagnose cancer but cannot diagnose stage. My use of the terminology of cocarcinogenesis versus promotion is different. Cocarcinogens need to both be present to even initiate a genetic change in the cells. Promoters move the cells into the next steps in the formation of the tumor. Thus the terms apply to different steps and may play a different role especially in their actions.

Pages 30. While I believe that review of the other data sets are important, there are many limits especially to the recent data bases that may not solve the EPA's needs even though our paragraphs suggest that they will. There are so many factors to control such as long, possibly 30 years of dose data required, latency periods also as long as 30 years or so, population mobility, other dietary and disease factors and even competing risk considerations since As causes several cancers with different latencies most of which have shorter times to onset than for bladder cancer, that EPA will face a challenge in trying to equate any differences to specific factors in each data set.

Page 32-34 Most of the discussion provided by JY in these pages should be summarized to say only that EPA should examine all of the studies to see the advantages and disadvantages of each. The details provide too many potential questionable assumptions by the writer that will only engender criticism of the report and we would like to avoid that. For example, the example of the integrated study that is proposed is methylmercury in utero and neurological effects in children. The exposure periods and the latency of the outcome are so short for this example compared to what EPA needs for bladder cancer and As it is not subject to any of the same constraints that the As studies are. For As, EPA needs a population that stayed in one place for about 80 years with little immigration, had limited sources of water, and had little medical care that could influence the diagnosis of the cancer. They then needed estimates of the As level in the water throughout that period. Since bladder cancer is not very common, EPA must be sure that the population is large enough, has had a long follow up and has had sufficient exposure to As to have at least 80% power to show an effect if indeed one exists. If one data set is best for determining a dose response then that data set should be used just as is done for radiation using the Japanese database. US populations are especially poor because they migrate so frequently.

The discussion of integrated studies has not only focused on an exposure and outcome that are short and, therefore, of limited relevance but the suggestion in the middle paragraph on page 33 is not appropriate for those studies. The criteria for integrated studies have been set out by the several groups including the WORLD Cancer Research Fund and they do not approach the problem according to the exposure level of the population. All studies with sufficient

exposure data are included in the analysis, studies are kept separate by design, all are subject to rigorous assessment of the potential for bias of reporting , etc. None of this is relevant to tell the agency. Rather we should not be determining methodologies but suggesting they look at other databases both for consistency of findings by dose and the sensitivity of their conclusions related to a single population.

This is probably not the appropriate venue to try to change EPA policy as is suggested on page 34. That is best referred to SAB for review of basic science procedures and decision-making of EPA. We are reviewing a document from within offices of EPA, which must adhere to the current guidelines.

Page 35. To actually determine that children are more susceptible than adults you have to show that their risk is higher than adults given the same dose. The paragraph has dose and age intermingled. We have also brought in the concept of reproductive outcomes but that may relate to the susceptibility of tissues at different ages. These concepts really need to be clarified as they do not indicate the same “susceptibilities” at early ages.

Page 37. lines 41 TR is correct. There is a thesis by Dr. Wu (not published) that found differences in DNR repair related to As and other exposures in the Taiwanese population.

Page 43 and 45. What does it mean to have to different forms of the equation picked by NRC versus EPA as the best fit. Is one of the two in error or can't you distinguish between the two?

Page 44. line 6 and 7 It would be helpful to explain who these people are with perhaps a title.

Page 47. Sha is correct about maternal mortality as well. But it is important to check on the sex distribution of infant and childhood mortality as well. As SH suggests immigration of males at a certain point in the history of the island could have increased the male ratio. However, a check is warranted.

Page 48. line 3 Is the 3X difference in exposure a measure of differences in water intake or what?

Attachment 1

Schema of iAs Metabolism in the Rat and Human

Rat

Human

