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Hello Arsenic Panel Members:

In preparation for the Conference Call on Feb. 23 to continue our discussions of the Panel's responses to the EPA Charge questions, I have tried to develop changes to the text in response to comments made by panel members related to Comment C1 in Section 3.4.1. Use of animal data for DMA^V. I would appreciate it if you could review the proposed changes and let me know if you agree or suggest other changes. In particular, I would appreciate it if the individuals who authored the comments could let me know if the proposed changes are responsive. Thank you in advance for your review/response.

Regards,
Michele Medinsky

The comments, response and suggested changes are indicated below and in an attached Word document.

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).

Response: I propose we insert the text below indicated in blue.

Issues that panel members consider important to discuss in EPA's Science Issue Paper are discussed in more detail below and in [Section 3.2.1](#). These issues relate to the toxicokinetic and toxicodynamic differences between rats and humans in response to arsenic exposure, the use of rodent bladder tumor models in general, and issues in the use of rodent data for human risk assessment.

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)

Response: I propose deleting the sentence indicated in yellow highlight from this section:

Data illustrating the mode of action for DMA^V as a bladder carcinogen in rats seem quite convincing. However, rats are much more sensitive to DMA^V in carcinogenicity testing than the mouse (Rossman, 2003; Arnold, et al., 2003). Several- toxicokinetic and toxicodynamic differences between rats and humans have also been reported after arsenic exposure. For example, arsenic methylation in rat liver hepatocytes proceeds at a faster rate than in human hepatocytes; and rats have a considerably slower whole body clearance of DMA than humans. This slower whole body clearance in rats is because a significant portion of DMA is retained in the erythrocytes of rats (Vahter, et al., 1984). There is a 15 to 20 fold higher binding of arsenic to rat hemoglobin than to human hemoglobin (Lu, et al, 2004). Human bladder tumors are primarily transitional cell carcinomas, and rat bladder tumors are reported to bear some similarity in pathology to low-grade papillary tumors that occur in humans; however, they are not similar to invasive human bladder tumors that display high grade malignancy (Cohen, 2002). The foregoing, taken together, illustrate known substantial metabolic, The pharmacokinetic and pharmacodynamic differences between rats and humans and should be thoroughly discussed in the final EPA documents as these data indicate that the rat may likely be considerably more sensitive to developing bladder cancer than humans after exposure to DMA^V.

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.

Response: I propose adding the text indicated in blue to this section and deleting the sentence highlighted in yellow as suggested by Dr. Stylo.

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

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)

Response: For Comment 19 I propose that the text indicated in blue be added and the text highlighted in yellow be deleted. For Comment 20, the reference to the FQPA has been deleted and the words “interspecies safety factor “ have been substituted. I would appreciate comments regarding the strength of the evidence for reduction of safety factors for the toxicokinetic and toxicodynamic portions of the safety factor.

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

Comment 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)

Response: I propose that the words in blue be added and the yellow highlighted words be deleted.

The Agency should also discuss in its Science Issue Paper, **similarities and** differences between rats and humans in the development of bladder tumors, and how these differences impact interspecies extrapolation. **For example, urinary bladder tumors in rats occur very late in life**. Studies suggest that in rats it takes two or more years of continuous high dose exposure to DMA^V to induce these tumors. This would equate to a human **being** developing cancer very late in life as well. The Science Issue Paper should specifically discuss the similarities and differences in the time for induction of DMA^V related tumors in rats with the pattern observed with humans and arsenic associated urinary bladder cancer.

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

Response: I propose the highlighted text be deleted.

EPA'S Science Issue Paper should also discuss general issues associated with rat urinary bladder cancer. One such issue is the relationship between the non-specific induction of tumors and high concentrations of arsenic in the urine. Also, there is a need to address evidence that simple enhancement of proliferation is not associated with carcinogenesis in many tissues. Studies by Gur et al. (listed on page 97 of the DMA MOA Science Issue Paper) on the carcinogenicity of DMA^V were never published and thus cannot be critically evaluated by the Panel. The Science Issue Paper notes that the Gur studies in rats and mice are key bioassay studies. Reliance on these studies would be stronger if the studies had the benefit of peer review.

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)

Response: I am going to have to ask for help on this comment. Can Dr. Waalkes or Dr. Rossman edit the paragraph below as appropriate.

EPA's Science Issue Paper is critical of the transplacental model for inorganic arsenic carcinogenesis because the work was done in a sensitive strain of mouse (C3H) that develops a significant background level of tumors in certain tissues. Implicit in this criticism is the assumption that the presence of a high spontaneous tumor rate in the organ of interest makes the interpretation of the animal data difficult. That difficulty would extend to the ability to estimate the proportion of human tumors, if any, that could be attributable to low exposure to a specific contaminant such as iAs. However, it is well known that all cancers in rodent and human tissues can occur spontaneously. Thus, it could be argued that no rodent carcinogenesis studies could be used to assess human carcinogenicity. Clearly, this is not the case as rodent studies are used routinely for human risk assessment. The EPA's position on the issue of using a sensitive strain to extrapolate to humans should be expanded and clarified in the Science Issue Paper especially as it relates to arsenic. As part of this clarification, requirements for target site concordance between human and rodents in order to validate a rodent bioassay and the relative weight placed on fatal versus not fatal cancers should be discussed as they apply to arsenic.