



November 15, 2010

Dr. Angela Nugent, Designated Federal Officer
US EPA Science Advisory Board (1400R)
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Need to Include and Evaluate Relevant Recent Literature in the 2010 IRIS Arsenic Assessment

Dear Dr. Nugent:

In 2007, the United States Environmental Protection Agency (US EPA) Science Advisory Board (SAB) released its report on the "Toxicological Review of Inorganic Arsenic," which focused on evaluating arsenic carcinogenicity for the Integrated Risk Information System (IRIS) (2005 IRIS Arsenic Assessment) (US EPA, 2005). In the 2007 Report, the SAB Arsenic Panel noted that there were several areas in which further research was needed to address outstanding scientific issues (SAB, 2007). Two issues that were specifically acknowledged as needing further study were:

- The need to more fully address arsenic's carcinogenic mode of action (MOA) and the possible existence of a threshold; and
- The need to evaluate available epidemiological data in an integrative analysis to assess the validity of the quantitative risk estimates derived solely from the Taiwan data.

In 2010 – about three years after the SAB report – the National Center for Environmental Assessment (NCEA) and the Office of Water (OW) issued a revised version of the IRIS report (US EPA, 2010). The 2010 IRIS Arsenic Assessment specifically reports the cutoff for reviewing literature as August 2007, ignoring important new research published between August 2007 and the date of publication of the 2010 assessment, as well as over 100 studies published between 1999 and 2007. It is important that US EPA incorporate the new information into its analysis to ensure that the final arsenic IRIS evaluation contains state-of-the-art information

Specifically, the analysis of the MOA studies published until 2007 lacked rigor; studies were listed in an appendix, but there was no meaningful attempt to synthesize these data. Information on inorganic arsenic's MOA is critical because such understanding informs decisions about low-dose extrapolation. Since 2007, several studies have been published that provide evidence that arsenic bladder carcinogenicity involves cytotoxicity followed by regeneration (Suzuki *et al.*, 2010; Yokohira *et al.*, 2010; Nascimento *et al.*, 2008). Additionally, there is ongoing work sponsored by the Electric Power Research Institute (EPRI), in which US EPA had collaborated, to establish a biologically based dose-response model for arsenic. And while this work is not complete, initial research related to the project has shown that low doses of arsenic are associated with protective effects which may indicate a threshold (Gentry *et al.*, 2010). A list of key studies that have not been reviewed as part of the IRIS assessment, but provide important insights on arsenic MOAs, is attached to this letter.

In April 2010, an SAB Workgroup was convened to assess the completeness of the 2010 IRIS Arsenic Assessment, both from the perspective of evaluating the sufficiency of revisions proposed by the 2007 SAB Arsenic Panel Report and ensuring that remaining scientific issues are adequately

addressed before draft finalization. Despite this responsibility, the SAB Workgroup addressed MOA information in a very limited way. There was neither attempt to conduct a more complete synthesis, nor any attempt to understand how new data (left un-reviewed in the 2010 IRIS Arsenic Assessment) might affect decisions about low-dose extrapolation. The SAB Workgroup simply notes that the uncertainty should be acknowledged. Specifically, the Workgroup states, "The SAB recommends that this complexity and limited understanding of the MOA of arsenic should be openly acknowledged in the 2010 draft assessment" (SAB, 2010a). The failure to address this important issue was both the result of a narrow charge (which did not specifically ask for comment on MOA information) and an unwillingness to go beyond the charge question. Moreover, as acknowledged by one of its members, the members of the SAB Workgroup lacked sufficient expertise to conduct a full review of new data (SAB, 2010b).

The SAB Workgroup was more responsive to the epidemiological analysis presented in the 2010 IRIS Arsenic Assessment and directly acknowledged that cutting off the extensive literature review at 2007 was problematic. The Workgroup report states:

The SAB recognizes that the assessment cannot be continually updated with every newly published paper and it is not the purpose of IRIS to provide real time summaries of advancing science. However, given the large amount of ongoing research on the health effects of arsenic, the SAB has concerns about the 2007 cutoff. In order to ascertain if new studies will impact the 2010 assessment, EPA should consider including an addendum or appendix describing major epidemiology studies published since 2007 (*i.e.*, those studies that can influence the dose-response assessment due to large sample size or effect estimate that is substantially different from that estimated by Chen *et al.* (1988, 1992)). (SAB, 2010a)

While the Workgroup is clear that more recent literature should be reviewed, the offered solution was to present important new studies in an appendix. This response does not meet the intent of the 2007 SAB, which specifically recommended that an integrative analysis of relevant studies be conducted to understand what the available literature collectively supports, and to assess the validity of the quantitative risk estimates generated by the sole use of the dataset from Taiwan. The 2010 IRIS Arsenic Assessment did not conduct an integrative analysis, and ignored existing meta-analyses, including one which was updated in comments to the SAB Workgroup on June 16, 2010 (Mink *et al.*, 2008, 2010; Chu and Brown, 2006, 2007). These serious oversights were not acknowledged by the 2010 Workgroup, let alone remedied. Moreover, like the MOA scientific literature, there are several recent epidemiological studies that provide important information about arsenic's dose response that are not included in the 2010 IRIS Arsenic Assessment. Overall, many of these studies (*e.g.*, Chen *et al.*, 2010; Chen *et al.*, 2009; Meliker *et al.*, 2010) show no consistent statistically significant dose-response relationship between arsenic exposure at low doses (*i.e.*, less than 100 µg/L) and bladder and lung cancer.

Given that recent literature offers important new insights that can affect the quantitative risk estimates of arsenic potency, and all regulations stemming from future arsenic-related risk assessments, it is imperative that state-of-the-art information underlie the 2010 IRIS Arsenic Assessment. Ignoring important new literature that stands to better inform arsenic potency estimates compromises the quality of the 2010 IRIS Arsenic Assessment and falls short of the IRIS mission "to provide high quality human health risk information to EPA's Programs and Regions that ensures that the Agency's actions protect the public health" (US EPA, 2009).

The above comments are my own, prepared with the support of Organic Arsenical Products Task Force.

Sincerely,

Barbara D. Beck, Ph.D., DABT, FATS, ERT
Principal

Key MOA Literature not Considered in the 2010 IRIS Arsenic Assessment

1. Yokohira, M; Arnold, LL; Pennington, KL; Suzuki, S; Kakiuchi-Kiyota, S; Herbin-Davis, K; Thomas, DJ; Cohen, SM. 2010. "Severe systemic toxicity and urinary bladder cytotoxicity and regenerative hyperplasia induced by arsenite in arsenic (+3 oxidation state) methyltransferase knockout mice. A preliminary report." *Toxicol. Appl. Pharmacol.* 246(1-2):1-7.
2. Clewell, H. [Hamner Institutes for Health Sciences]. 2010. "Modeling of Early Key Events Based on Genomics and Potential Applications for Nuclear-receptor-mediated Toxicity." Presented at Texas Commission of Environmental Quality's Alliance for Risk Assessment Workshop, Austin, TX, March 16-18.
3. Gentry, PR; McDonald, TB; Sullivan, DE; Shipp, AM; Yager, JW; Clewell, HJ III. 2010. "Analysis of genomic dose-response information on arsenic to inform key events in a mode of action for carcinogenicity." *Environ. Mol. Mutagen.* 51(1):1-14.
4. Suzuki, S; Arnold, LL; Pennington, KL; Chen, B; Naranmandura, H; Le, XC; Cohen, SM. 2010. "Dietary administration of sodium arsenite to rats: Relations between dose and urinary concentrations of methylated and thio-metabolites and effects on the rat urinary bladder epithelium." *Toxicol. Appl. Pharmacol.* doi:10.1016/j.taap.2009.12.026.
5. Yager, JW; Clewell, HJ; Thomas, RS; Gill, G; Wagner, H; McKim, JM; Wilga, PC; Gentry, PR; Cohen, SM. 2010. "Evaluation of genetic changes in human primary uroepithelial cells following exposures to arsenite and its methylated metabolites." Poster presented at Society of Toxicology 49th Annual Meeting, Salt Lake City, Utah, March 7-11.
6. Beyersmann, D; Hartwig, A. 2008. "Carcinogenic metal compounds: Recent insight into molecular and cellular mechanisms." *Arch. Toxicol.* 82(8):493-512.
7. Kitchin, KT; Wallace, K. 2008. "Evidence against the nuclear *in situ* binding of arsenicals – oxidative stress theory of arsenic carcinogenesis." *Toxicol. Appl. Pharmacol.* 232(2):252-7.
8. Kenyon, EM; Klimecki, WT; El-Masri, H; Conolly, RB; Clewell, HJ; Beck, BD. 2008. "How can biologically-based modeling of arsenic kinetics and dynamics inform the risk assessment process? - A workshop review." *Toxicol. Appl. Pharmacol.* 232:359-368.
9. Salnikow, K; Zhitkovich, A. 2008. "Genetic and epigenetic mechanisms in metal carcinogenesis and carcinogenesis: Nickel, arsenic, and chromium." *Chem. Res. Toxicol.* 21(1):28-44.
10. Suzuki, S; Arnold, LL; Ohnishi, T; Cohen, SM. 2008. "Effects of inorganic arsenic on the rat and mouse urinary bladder." *Toxicol. Sci.* 106(2):350-63.
11. Sykora, P; Snow, ET. 2008. "Modulation of DNA polymerase beta-dependent base excision repair in cultured human cells after low dose exposure to arsenite." *Toxicol. Appl. Pharmacol.* 228(3):385-94.

12. Fry, RC; Navasumrit, P; Valiathan, C; Svensson, JP; Hogan, BJ; Luo, M; Bhattacharya, S; Kandjanapa, K; Soontararuks, S; Nookabkaew, S; Mahidol, C; Ruchirawat, M; Samson, LD. 2007. "Activation of inflammation/NF- κ B signaling in infants born to arsenic-exposed mothers." *PLoS Genet* 3(11):e207.
13. He, XQ; Chen, R; Yang, P; Li, AP; Zhou, JW; Liu, QZ. 2007. "Biphasic effect of arsenite on cell proliferation and apoptosis is associated with the activation of JNK and ERK1/2 in human embryo lung fibroblast cells." *Toxicol. Appl. Pharmacol.* 220(1):18-24.
14. Kumagai, Y; Sumi, D. 2007. "Arsenic: Signal transduction, transcription factor, and biotransformation involved in cellular response and toxicity." *Annu. Rev. Pharmacol. Toxicol.* 47:243-262.
15. Lu, M; Wang, H; Li, XF; Arnold, LL; Cohen, SM; Le, XC. 2007. "Binding of dimethylarsinous acid to cys-13alpha of rat hemoglobin is responsible for the retention of arsenic in rat blood." *Chem. Res. Toxicol.* 20(1):27-37.
16. Yang, P; He, XQ; Peng, L; Li, AP; Wang, XR; Zhou, JW; Liu, QZ. 2007. "The role of oxidative stress in hormesis induced by sodium arsenite in human embryo lung fibroblast (HELFL) cellular proliferation model." *J. Toxicol. Environ. Health A.* 70(11):976-83.

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