



November 15, 2010

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

Dear Dr. Nugent:

I am writing to raise concerns about the United States Environmental Protection Agency (US EPA) 2010 draft "Toxicological Review of Inorganic Arsenic" (2010 IRIS Draft) (US EPA, 2010) and its review by the Science Advisory Board (SAB). The SAB meeting scheduled for November 22, 2010, is set to consider the report of the Arsenic Workgroup on its assessment of the sufficiency of US EPA's responses to the review of the 2005 draft "Toxicological Review of Inorganic Arsenic" (2005 IRIS Draft) (US EPA, 2005) that was expressed in SAB's 2007 review report (SAB, 2007).

In particular, it is important to note that the 2010 IRIS Draft proposes a value for the oral unit risk for assessing arsenic carcinogenicity of  $25.7 \text{ [(mg/kg-d)}^{-1}]$  (US EPA, 2010). This value is 4.5-fold greater than the value of that appeared in the 2005 IRIS Draft [ $5.7 \text{ (mg/kg-d)}^{-1}]$  (US EPA, 2005). This represents a major change from the earlier value that is already in question, and its implementation would have profound impact on the costs of providing drinking water at traditionally accepted risk levels for much of the US population.

It is critical that the change in cancer potency represent a scientifically necessary and scientifically supportable alteration of the arsenic carcinogenicity assessment, and not just the adoption of a possible point of view, especially because such an alteration is so consequential. For the new value to have credibility, it is imperative that the underlying analytical bases for the change from the 2005 value to the 2010 draft unit risk value proposal be thoroughly understood and thoroughly subjected to rigorous scientific review. There are several contributing factors that have affected the changed calculations from 2005 to 2010 – these must be evaluated for their basis and impact not only individually, but also *collectively*. That is, the review process must ask whether the final resultant value of the oral slope factor (and not just separate elements of its calculation) is credible and in accord with scientific understanding.

I wish to call your attention to two matters of concern. First, the present Arsenic Workgroup's review clearly states that it was *not* asked to conduct a *full* review of the 2010 IRIS Draft, and indeed it has not done so. The Workgroup's report states:

In response to this request, the SAB convened a workgroup of the chartered Board to comment on the agency's charge questions that focused on three areas: evaluation of epidemiological literature; dose-response modeling approaches; and the sensitivity analysis of the exposure assumptions used in the risk assessment. The SAB was not asked to conduct a full peer review of the assessment, including EPA's calculation of the cancer risk estimate. (SAB, 2010, p. 4)

Instead, its review focused on the particulars of those factors (and only those factors) that US EPA chose to modify from its 2005 to its 2010 analysis, namely (1) the inclusion (and value of) a measure of dietary intake of arsenic in addition to that coming from water, and (2) the assumed amount of water consumed for US *versus* Taiwan populations. In short, even for these limited factors, there was no overall review of the resultant recalculated oral cancer unit risk, its overall justification, or its

scientific credibility. The new result is sufficiently altered from its 2005 predecessor that a thorough review by outside scientists with the full range of relevant expertise, that asks whether the proposed potency can be scientifically supported, is required.

It is evident from the sensitivity analyses in the 2010 IRIS Draft (US EPA, 2010) that the values chosen for these factors can markedly affect the calculated potency. The impact would be even greater if the differences in the factors between the 2005 analysis and the 2010 baseline analysis were included in the sensitivity assessment (but that assessment was limited in only examining alternative values considered within the context of the 2010 analyses). Moreover, the Panel expressed concern that sensitivity to *combinations* of assumptions was not assessed. When discussing the choice of a reference population, the Workgroup stated that "EPA might consider whether any combinations of these parameter variations should be examined – *e.g.*, using different non-water intake values in combination with a different reference population" (SAB, 2010, p. 10). Because different assumed values can affect curve shapes, the simultaneous consideration of combinations of assumptions can show sensitivity of the final answer in a way that factor-by-factor, one-at-a-time, evaluations cannot.

The second matter of concern is that the Workgroup found the justification for the dietary and drinking water assumptions inadequate, stating "Despite some effort to discuss drinking water consumption rates and sources of information for non-water arsenic intake rates, the reasons for some of the specific values chosen to be included in the sensitivity analyses are not clearly justified (SAB, 2010, p. 12-13)." Because of the evident importance of the values chosen in affecting the final cancer potency projection, it is important that the values be well justified. Before any document can be considered for finalization, SAB should review whether the changes US EPA may have made to address this call for better justification have been responsive, and SAB should evaluate the scientific credibility of the result, not merely acknowledge that discussions have been edited.

The Panel's report clearly expresses concern about the credibility of the final oral cancer unit risk as proposed in the 2010 IRIS Draft, calling for a "reality check" to see if the large risks projected for much of the US population from existing naturally occurring arsenic in drinking water can in fact be reconciled with known total cancer risks. It should be noted that the meta-analysis of Mink and coworkers on bladder cancer risks in populations exposed to low level arsenic concentration is informative in this respect: the relative risks (RRs) were not significant for populations exposed to arsenic in drinking water in the 0.5 to 150 µg/L range, including US populations (Mink *et al.*, 2008; Mink, 2010).

**In summary, therefore, any proposed final potency from US EPA ought to receive a full review, not just a review of its component assumptions, to ensure that it represents a defensible view that is compelled by evidence rather than set by choosing preferred assumptions.**

In my comments above, I have focused on specific changes that US EPA made to its dose-response analysis between 2005 and 2010, arguing that these US EPA *actions* have been reviewed incompletely. In previous opportunities for public comment on the arsenic analysis (Gradient, 2010; Rhomberg, 2010), I have focused on *inactions* – I have argued that important issues identified as critical in the 2007 SAB review, and some of the analyses the 2007 review proposed to address them, have not been taken up in the 2010 IRIS Draft, nor has this lack been noted by the present Arsenic Workgroup's review process. These include the quantitative impact of forcing fitted Taiwan dose-response curves to accommodate an outside reference population that in important ways is different from the study area itself, the lack of meta-analysis of US population arsenic studies (which collectively suggest no low-dose effect), and the question of reconciling linear low-dose extrapolation with mode of action data that strongly suggested nonlinearity to the 2007 SAB

reviewers. If the 2010 IRIS Draft is to be judged to have addressed the concerns of the 2007 SAB report, the way in which the revision deals with these issues— which are prominent features of the 2007 SAB review – needs to be thoroughly examined.

I urge the SAB to forthrightly debate the matters I discuss above. In my view, the SAB should conclude that any candidate for a final US EPA document that proposes a cancer oral unit risk as profoundly different from that proposed in 2005 should, in view of its major impact on arsenic risk management questions, receive a comprehensive review; this should not only review its component calculations, but should also assess whether the 2010 IRIS Draft as a whole is scientifically credible and compelling. Anything less will mire the risk management process in debate and doubt stemming from the questions that have remained unanswered or unreliably answered by the risk assessment review.

The above comments are my own, prepared with the support of the North American Metals Council.

Sincerely,

GRADIENT

Lorenz R. Rhomberg, Ph.D., FATS  
Principal

## References

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