Dear Mr. Miller -

I am contacting you to inquire about joining, as a member of the public, the upcoming teleconference on the EPA SAB draft report, "Assessments of carcinogenic effects of organic and inorganic arsenic" which I understand is scheduled for Jan. 24 1:30-4:00 pm.

By way of background / potential conflict of interest, I am a scientist at Dartmouth Medical School who is an active researcher in the arsenic toxicology field. I have active grants from NIEHS and NSF that involve studies of the molecular toxicology of arsenic, and also direct the Dartmouth Superfund Basic Research Program Project in which over two dozen faculty researchers collectively focus primarily on arsenic toxicology and epidemiology. I am aware of no other potential conflicts of interest with respect to this report.

I would also like to provide the following written comments for you and the committee to consider in response to your draft report:

1. Mechanism of action. We feel that endocrine disruption by As should be added as an important potential mechanism of action that could explain many of arsenic's adverse health effects in humans. My lab first reported that As can act as a potent endocrine disruptor, altering hormone-mediated gene regulation at very low (nanomolar) concentrations. We have demonstrated this both in cell culture and in vivo. Given that we have now shown As can disrupt all five steroid hormone receptors as well as the receptors for thyroid hormone and retinoic acid, we believe that this is an important mechanism of action of As that may contribute both to cancer and non-cancer risks such as diabetes, birth defects and reproductive / developmental problems, vascular and cardiovascular disease and other diseases. There are many known links between steroid receptor function and carcinogenesis. For example, previous studies by Slaga et al. in the mouse two-stage skin cancer model and by Wattenberg et al. in a mouse two-stage lung cancer model showed that glucocorticoids can suppress tumor formation, primarily by blocking tumor promotion. Similar studies in skin and lung cancer cell lines (see for example studies by Malkinson et al.) showed that glucocorticoids can suppress cell division and promote differentiation. However, in some lines that were resistant to anti-tumor effects of GCs, it was shown that the glucocorticoid receptor was mutated or alternatively spliced to render it inactive. These studies collectively demonstrated that GR normally suppresses carcinogenesis whereas loss of GR function is permissive to cancer progression. Thus, if As blocks GR function, as we have shown, this could contribute significantly to cancer risk. Interestingly, the two tissues in which the effects of GR on cancer were demonstrated, i.e., skin and lung, are two of the most important targets for As cancer risk in humans. Of course, it is well known that ER and other sex steroid receptors play a role in carcinogenesis in certain tissues as well.
2. Low dose extrapolation. The dose-response for biological effects of arsenic is complex as noted in the report. We have performed As toxicogenomics studies that show a striking shift in gene expression response between a relatively low, non-cytotoxic dose (5 μM) and and higher, cytotoxic dose (50 μM). Likewise, we recently reported additional endocrine disrupting effects that reveal a very complex, non-linear dose-response at very low doses (well down into the sub-micromolar range, equivalent in some cases to less than 1 ppb iAs) which may be informative regarding low dose extrapolation. Similar non-linear dose-responses have been observed for effects of As on endothelial cell response and angiogenesis as was cited in the draft report, as well as other examples. Thus, experimentally, the dose-response -- particularly at low, environmentally relevant doses -- is complex but clearly is non-linear and also clearly does not follow even the classic sigmoidal curve of toxicology dogma. In addition, arsenic is not a direct-acting genotoxin or mutagen, and therefore it does not seem appropriate on this basis to default to a linear low-dose extrapolation model when calculating low dose risk as discussed. On the other hand, the report implied that this might lead to choosing a threshold model, and in our view the agency should use extreme caution in doing so. There are clearly profound biological effects of very low level arsenic exposure, and these effects are sometimes opposite of those at high doses. For example, it is well established that arsenic can enhance cell growth in culture, endothelial tissue growth in vivo, and have other positive effects as discussed. But it is not at all clear whether these effects are beneficial, harmful, represent adaptive responses, or some combination. One could argue, for example, that in someone who might have nascent tumors or premalignant lesions, enhancing cell proliferation and/or enhancing vascularization might not be a good thing and could actually enhance cancer promotion or progression. Likewise, enhancing hormone-stimulated gene expression at low doses, as we have demonstrated in our studies, and in a range equivalent to U.S. drinking water levels, is not necessarily beneficial and could potentially lead
to pathophysiological effects in a number of different tissues. The
draft report also cited older studies suggesting that arsenic may be an
essential trace element. However, this is a controversial area, and
arsenic essentiality remains to be determined experimentally. The older
data in this regard are very weak, incomplete, and in some cases
entirely misleading as currently cited in some recent reviews. For
example, some of the key studies most often cited are merely abstracts
which have little or no experimental detail and, as far as we could
determine, were never published as full length or peer-reviewed papers.
These studies were also for the most part conducted in the 1970's in the
context of agricultural feed supplementation, and at a time when arsenic
measurements were crude. So their definition of "low arsenic" diets is
quite different from our current understanding of arsenic in food. For
example, some of these studies started with what they deemed a "low
arsenic" diet, then added high amounts of arsenic as a feed supplement.
They noted enhanced growth rate and other effects of As supplementation
that they cited as being beneficial. However, while rapid weight gain
can be argued to be of agricultural benefit, it is not at all clear that
this is physiologically beneficial in the context of human health, or
that absence of arsenic would be detrimental in this regard. We are
currently conducting studies in mice in which we have reduced total food
arsenic well below 1 ppb and will be examining these animals relative to
those with organic and inorganic arsenic in food versus iAs in water.
Hopefully others will also re-investigate these issues. Until such
studies are conducted under more modern conditions, we would urge
extreme caution in considering or citing this essentiality literature,
particularly in the context of establishing low dose toxicological
effects of arsenic.

Thank you for considering these comments. I commend the panel for their
thoughtful review of the EPA documents and their careful analysis of
this important topic.

Sincerely,

Joshua Hamilton