OAPTF

Organic Arsenical Products Task Force

Luxembourg-Pamol, Inc. • Drexel Chemical Company

April 20, 2010

Via E-Mail

Office of Environmental Information (OEI) Docket
Mail Code: 2822T
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Comments on the Draft U.S. EPA document "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-10/001); 75 Fed. Reg. 7477; Docket ID No. EPA-HQ-ORD-2010-0123

Dear Sir or Madam:

This letter is submitted on behalf of the Organic Arsenical Products Task Force (OAPTF).[1] We write to express our deep concern about aspects of the Science Advisory Board (SAB) Workgroup's April 6-7, 2010, review of a draft U.S. Environmental Protection Agency (EPA) document, "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-10/001).

As you know, a Notice of the public meeting of the SAB Workgroup to review the 575 page IRIS assessment of Inorganic Arsenic was published in the *Federal Register* only on March 1, 2010.[2] The OAPTF, by a March 10, 2010, letter to Dr. Maciorowski,[3] had requested the SAB to reschedule the meeting. The SAB denied the request in a letter of March 18, 2010.[4] For the reasons discussed in our March 10 letter, convening the April 6-7 Workgroup meeting on

[1] The OAPTF consists of Drexel Chemical Co and Luxembourg-Pamol, Inc., both registrants of pesticide products that contain monosodium methanearsonate (MSMA).

[2] 75 Fed. Reg. 9205 (Mar. 1, 2010).

[3] Letter to Mr. Anthony F. Maciorowski, SAB, from Lynn L. Bergeson, Esquire, Bergeson & Campbell, P.C. (Mar. 10, 2010). A copy of the letter is appended.

[4] Letter from Anthony F. Maciorowski, Ph.D., SAB, to Lynn L. Bergeson, Esquire, Bergeson & Campbell, P.C. (Mar. 18, 2010). A copy of the letter is appended.

such short notice to the interested public, including the MSMA registrants, contravened EPA's Public Involvement Policy, in allowing a wholly inadequate period for such interested persons to consider the 575-page IRIS assessment and prepare written comments for submission to the SAB. Nor did the schedule provide a realistic period prior to the meeting for the SAB Workgroup members to review thoroughly the issues in the 2007 report of the 2005 SAB panel, or to consider the public comments. Considering that none of the Workgroup members is, as reflected from the descriptions on the SAB website, an expert in relevant issues regarding arsenic, the members surely needed more than the time provided to become sufficiently familiar with the issues at stake, to conduct an adequate scientific review.

As the SAB elected not to postpone the meeting, the OAPTF submitted comments on March 29, 2010 -- too limited a time to address the document in the depth desired[5] and too limited a time, we believe, for the SAB to consider these and other comments prior to the meeting. OAPTF representatives attended the April 6-7 meeting and were disappointed to realize that the meeting proceedings themselves have raised further substantial concerns as to both substance and process, the key among which are noted here.

While some key issues go to science and others to process,[6] including responsiveness to EPA's original 2005 charge questions, many are a result of these two fundamental deficiencies in the review.

Together with the issues the OAPTF identified in its comments on the draft document, these comments point out pervasive flaws that throw into question the viability of the SAB review as a basis for EPA actions going forward.

Charge and Process Issues

Specific charge and process-related issues of concern to the OAPTF following the April 6-7 meeting include the following:

---

5 The OAPTF comment document specifically noted how the limited time period affected the scope of those comments. *See* letter to A. Maciorowski, *supra* note 3, at 4.

6 In some instances, of course, the line between science and process is blurred, and the OAPTF's concerns may go to both, even if addressed under one heading or the other.

- First, before the April 6-7 meeting was scheduled, the OAPTF and other interested stakeholders met with Dr. Paul Anastas and were assured by Dr. Anastas that the Workgroup was free to go beyond EPA's charge questions. Nonetheless, SAB Workgroup members appeared intent on limiting their discussions narrowly to the charge questions, apparently unaware of Dr. Anastas's suggestion that they were free to go beyond the charge questions.

- Even if the Workgroup wished to review issues beyond the charge questions, the meeting agenda did not leave time for discussion of any issue beyond the charge questions. The time provided, which was actually only one day, did not allow an appropriate chance to review issues within the charge questions. Thus, the Workgroup not only failed to review highly relevant issues beyond the charge, but it also failed to review appropriately issues within the charge.

- Despite clear directions to the effect that the charge was to evaluate whether the revisions to the draft IRIS document met the 2007 SAB recommendations, the Workgroup engaged in no parsing of specifics in this regard, nor in any critical analysis of most such recommendations (other than in approving the Taiwan exposure estimates). The Workgroup manifestly made no effort to articulate or understand the reasons that underlay the concerns expressed by the SAB in 2007, or to determine whether or how those concerns had been addressed. Instead, review of the document focused on the Workgroup's approving the choice of the Taiwan study, the linear model, data tabulation -- but not on a host of other significant issues. It appeared as if the Workgroup viewed its role as the role of an editor with the purpose of strengthening the document rather than a role of an independent scientific reviewer.

- Efforts by some Workgroup members to bring up legitimate discussion points -- *e.g.*, the adequacy of comparison of epidemiological studies, use of professional judgment *versus* data in identification of drinking water rates, uncertainties in the exposure assessment or the need for a "reality check" on risk calculations -- were turned into suggestions for editorial refinements. Questions of substance going to the adequacy of the response to the 2007 recommendations were lost in the process.

- Obviously peculiar statements by EPA either were reformulated by the chair to be slightly less odd (such as a statement that the cause of many lung cancers in the

U.S. is unknown) or simply allowed to stand (such as a statement that the Taiwanese population in the relevant time period did not consume much rice).

- Various further misstatements were permitted to stand. For example, it is incorrect that the reasoning as to the use of the reference population had been properly vetted in an issues paper, but reviewed by the 2005 SAB panel not provided in the docket. Similarly, a mischaracterization of prior SAB comments on the reference population also stood uncorrected. A statement made by a commenter that the Taiwan population had many elevated types of cancer was contradicted by EPA with no scientific basis. The Workgroup was not made aware publicly of a paper[7] that was handed to Dr. Shallal demonstrating the commenter's point was indeed supported by public literature.

- The chair seemed at times to over-step the traditional role of a chair. For example, the chair instructed panelists on how to present their points, occasionally jumping in and rephrasing those points, and unilaterally turning critiques into recommendations or clarifications unless a participant took immediate issue.

- The chair also seemed to rush the proceedings unnecessarily, and appeared to be governed more by a desire to meet a time deadline than to address conclusions in any depth. Similarly, the chair was markedly deferential to EPA, throwing out lifelines in sensitive or troublesome areas of inquiry, and never encouraged the airing of contrary or more balanced views, even in an exploratory way.

- Evidently, materials that had been submitted to the IRIS docket, and or to the SAB website were not provided to the panel members before the meeting, and the panel members did not appear to be aware of such documents. When questioned about the docket issue at a break in the meeting, Dr. Shallal responded that the panel should not be compelled to review all of the comments, most of which was surprisingly characterized by Dr. Shallal as irrelevant to their charge. Thus, submitted comments were ignored during the Workgroup discussions. It was unclear whether the materials from the IRIS docket would be shared with panel members, although the *Federal Register* notice stated that this would occur.

---

[7] Tsai, S-M; Wang, T-N; Ko, Y-C. (1999). Mortality for certain diseases in areas with high levels of arsenic. *Arch Environ Health* 54(3):186–193.

- A day and a half-long period of discussion among panel members in private before the start of the public meeting appears to have occurred. Apparently the meeting discussion included comments between the chair and the panelists, since a visible effort was made to read at least a nominal version of the meeting results into the record in the public part of the meeting. We learned of this private session from the chair, who confirmed that she and her colleagues had been in the meeting room together for that period, prior to the start of the public meeting.

- A March 25, 2010, letter (a copy of which is attached), submitted by some of the 2007 SAB panel members, outlining concerns over the contents of the draft IRIS document, was presented as a mere technical correction of a listing of the reviewers, despite the letter being quite explicit as to EPA's lack of a systematic review of the epidemiological studies and lack of a critical analysis of the mode of action (MOA) studies. Nor was the letter presented as declining to concur with any part of the draft report under review.

- Entire portions of the 2007 SAB recommendations were not discussed at all -- *e.g.*, the need for an "integrative" analysis of the U.S. low-dose studies, the need for comparison with results from other studies from outside southwest Taiwan. The overlooked portions essentially were swept together as an answer to an unasked question -- whether any single study should replace the Taiwan study as the major study, thus avoiding discussion of the questions the 2007 panel actually had posed.

- From the information provided about the Workgroup members on the SAB website, there are significant questions as to the expertise represented on the panel. No panelist had expertise in carcinogenesis or MOA; none had expertise in cancer dose-response modeling or cancer risk assessment guidelines. The main (lead) panelist for modeling professed a lack of statistical and modeling expertise. As evidenced by confusion on the question of the misclassification impact in non-dichotomous studies, most panel members also lacked a sufficient level of expertise in epidemiology, and in the complicated issues regarding arsenic carcinogenicity.

- Overall, the Workgroup was extraordinarily incurious about what was really the right interpretation of the difficult issues presented; about what prompted the 2005 SAB panel, in their 2007 report to ask for changes or expanded treatment in various areas; or about whether the revised document succeeded at resolving the

relevant issues. The general tone of the meeting suggested that the Workgroup's job was to approve the revised IRIS report after a quick run-through; to reiterate support for the aspects of which they approved; and to act as only in the limited role of editors in clarifying how the document expressed itself, rather than as substantive reviewers. The Workgroup accepted EPA's presentation without discussion and without questioning the absence of new analyses. One Workgroup member stated that the most important task for EPA was to justify the values being used. A perceived lack of time to discuss nearly any issue (other than the Taiwan exposure estimates) characterized the meeting overall.

- Last but not least, the Workgroup members completely ignored the verbal comments that were made by expert scientists before the Workgroup discussions.

Science Issues

Specific science-related issues of concern to the OAPTF in the wake of the April 6-7 meeting include the following:

- In focusing nearly exclusively on the Taiwan data, the Workgroup apparently endorsed EPA's refusal to conduct a meta-analysis of its own or to review other recent meta-analyses, such as the Mink *et al.* paper referenced in the OAPTF comments. In fact, the Workgroup's discussions completely ignored the existence of the Mink *et al.* meta-analysis. It was completely dismissed by Dr. Preuss in his comments, stating that all meta-analyses invariably come to an estimate of zero risk by averaging positive and negative results. This completely ignores the information that these ten studies included in the meta-analysis all come up with an estimated relative risk for low arsenic exposures of less than 1.0.

- Like the draft IRIS report, the Workgroup overlooked the relevance of newer, post-2007 literature on MOA, which erroneously was characterized as "mechanism of action." For example, the Workgroup failed to consider the ongoing work in the lab of Dr. Sam Cohen, in support of his demonstration that the MOA for inorganic arsenic is indeed known. The Workgroup seemed to adhere inflexibly to a notion of "multiple MOAs." Importantly, however, these various MOAs were not brought up for discussion. The Workgroup did not discuss the obvious need to perform a critical and complete analysis of the existing MOA studies (as had been requested by the prior SAB), nor did it appear

to recognize that simply listing the studies does not constitute such a critical analysis.

- The problematic reliance by the draft report, and also by the Workgroup, exclusively on the data from southwest Taiwan, was exacerbated by issues about the appropriateness of selecting a reference population outside the study area. The panel did not adequately probe how EPA chose and ran the linear model in question, nor did the panel discuss the reasoning or rationale in the 2005 EPA issues memorandum on which the choice of the reference population was based. The question of whether the outside reference population was comparable to the study area population in all but arsenic exposure (a required assumption for its use) was not brought up for discussion, despite a host of legitimate scientific questions that have been raised in this regard, including in oral comments at the meeting.

- Like the draft report, the Workgroup failed to address the 2005 SAB panel recommendation about the need for a proper sensitivity analysis of the dose-response evaluation of the Taiwan data, including changes in several critical parameters simultaneously. In particular, there was no discussion whatever about the effects of using no outside reference population combined with a nonlinear model.

- The Workgroup failed to discuss the role of true threshold models in the sensitivity analysis and did not seem to understand that the modeling used by EPA was not designed to detect a threshold if such existed. Yet another omission was the Workgroup's failure to discuss margin of exposure analysis using a point-of-departure, such as a benchmark dose.

- The Workgroup focused enormous attention on the least consequential aspect of the exposure estimates for the Taiwanese population (non-water aspects and the amount of water consumption), expressing great concern that values truly representative of the local population be used, yet at the same time did not address whether the corresponding intake values should be assumed to be equal in the study area and the largely urban outside reference population.

- Overall, the Workgroup scarcely discussed substantive points made by commenters, devaluing the meeting accordingly as a forum. The minimal effort at refuting isolated points demonstrated a lack of understanding of the issue(s)

involved. For example, one of the commenters (a Ph.D. epidemiologist and assistant professor of epidemiology at a research university), in the 5-minute public comment session, described how, based on fundamental epidemiological principles, it was incorrect to conclude that the impact of exposure misclassification would necessarily result in findings of no association between exposure and disease. This was an important point, because it countered the assertion that the Taiwan results would be even stronger if the exposure had been measured more accurately. Nonetheless, the incorrect statement that no association was a more likely finding in the case of exposure misclassification was subsequently reiterated by a Workgroup member, as if the commenter's presentation had not occurred.

- There was no discussion regarding the appropriateness of a linear extrapolation, even though the 2005 SAB concluded that the evidence for all possible MOAs was non-linear and likely involved a threshold.

- The draft IRIS report includes literature only until 2007 (included) with very few papers from 2008. The Workgroup appeared singularly unconcerned about the potential relevance or impact of the post-2007 studies in general, nor did they make any apparent effort even to articulate criteria for identifying which of the newer studies should be included in the report. The literature that has been published since 2007 is very important to these specific issues, because substantial research has been going on to address the questions presented in the 2007 SAB report. Thus, the state-of-the-art is missing from the document. Nevertheless, the Workgroup members did not find that missing such an important period of research (over two years) was a problem. Moreover, a substantial amount of literature is missing from the period before 2007.[8]

[8] Submitted as a separate comment to this document by the OAPTF is a listing of many of these data.

For the many reasons noted above, the OAPTF left the meeting profoundly dismayed by the lack of rigor demonstrated throughout the course of the proceedings. The future of the IRIS report and the potential impact it may have on future regulatory developments involving MSMA products make it essential that the above-described deficiencies in science and process be addressed promptly -- and certainly before a final report is issued.

Sincerely,

M. Eldan

Michal Eldan, Ph.D.

Attachments

cc: The Honorable Paul Anastas, Ph.D. (w/attachments) (via e-mail)
Anthony F. Maciorowski, Ph.D. (w/attachments) (via e-mail)
Vanessa Vu, Ph.D. (w/attachments) (via e-mail)
Steven P. Bradbury, Ph.D. (w/attachments) (via e-mail)
Peter W. Preuss, Ph.D. (w/attachments) (via e-mail)
Sue Shallal, Ph.D. (w/attachments) (via e-mail)
Lynn L. Bergeson, Esquire (w/attachments) (via e-mail)