UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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THE ADMINISTRATOR

Dr. M. Granger Morgan
Chair
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Dr. Morgan:

Thank you for providing me with the recent Science Advisory Board review of the *Framework for Inorganic Metals Risk Assessment, Peer Review Draft* (EPA-SAB-06-002). The U.S. Environmental Protection Agency appreciates the SAB Metals Risk Assessment Framework Review Panel's many thoughtful and constructive recommendations.

The framework authors, in coordination with EPA's Risk Assessment Forum, are in the process of addressing the recommendations and will be implementing many of the Panel's suggestions. The Office of Research and Development has prepared a detailed response to the major recommendations (enclosed) that were highlighted in your cover letter and executive summary.

Again, thank you for your efforts in reviewing the draft framework. I look forward to working with you and the SAB to further develop this important document.

Sincerely,

Stephen L. Johnson

Enclosure

cc: Dr. Deborah L. Swackhamer, Panel Chair
Dr. Vanessa T. Vu, SAB Staff Office Director

Response to SAB Recommendations on the Framework for Inorganic Metals Risk Assessment, Peer Review Draft

In February 2005, a panel of the Science Advisory Board met to review the draft *Framework for Inorganic Metals Risk Assessment* and comments from the public and stakeholders on the draft Framework. The SAB Metals Risk Assessment Framework Review Panel was composed of scientists representing a broad range of expertise in various aspects of human health and ecological risk assessment for metals and metal compounds and was representative of academia, the private sector, and federal and state governments.

The review panel report provides general support for the overall thrust and scope of the Metals Framework to allow for consideration of the unique properties of metals and the broad spectrum of physical and chemical properties, exposures, and effects among metals and metal compounds. However, the review panel recommended major revisions to ensure that the Framework has long-term value to Agency risk assessors. It recommended that the Framework be restructured to improve the clarity of its overall purpose, as well as a number of areas where improvements in the balance of discussion among the various topics were needed. It suggested a number of technical revisions and corrections to improve the precision and clarity of discussions. In responding to the charge questions, the review panel organized its comments into short-term items (those it believes can be addressed in the Framework in six months or less) and long-term items that it thinks will require more time to implement but nonetheless warrant acknowledgment in the Framework.

The responses below are structured around the four major comments outlined by the SAB in its cover letter and include, as appropriate, responses to some of the major recommendations outlined in the executive summary and body of the review panel report. The Agency plans to carefully consider all of the comments from the SAB and incorporate them as deemed appropriate into a revised document.

Summary of Comments and EPA Response

1. **The purpose of the Framework is unclear. The document attempts to serve as a description of basic scientific principles as well as a practical guide for risk assessors. To serve these two purposes, the document requires revision to provide a more balanced presentation of scientific principles and risk assessment guidance. The document should also clearly differentiate the following: *the Framework for assessment, examples to illustrate and clarify Framework issues, and specific instructions for risk assessors.***

EPA agrees and recognizes the need to restructure the Metals Framework. On the one hand, the Agency is often in a position in which its guidance documents, by necessity or choice, have multiple purposes. In the case of metals, however, the expansiveness and complexity of the underlying science, including the many tools and methods available in varying stages of development, coupled with the breadth of the Framework covering both human health and ecological risk assessment, made it challenging to strike an appropriate balance in providing risk assessors with targeted but representative information and guidance on the state of the science and how it might be used in the context of Agency risk assessment practices.

Thus, in recognition of the SAB's comments, the Agency plans to restructure the document to focus specifically on a set of guiding principles based on the unique attributes of metals and how these metal-specific attributes and principles may then be applied in the context of existing EPA risk assessment guidance and practices. Discussions related to specific tools and methods (currently located in Section 4) will be scaled back significantly. That is, in instances in which a particular tool or method is discussed, it will serve to illustrate a particular principle and be considered in the context of EPA hazard and risk assessment rather than as a comprehensive discourse on the applications and limitations of that given tool (or related approaches), as is currently the case. The rationale for this restructuring is to develop a final Framework document that would be of long-term value to EPA and would not be subject to frequent modifications as the supporting science evolves. To complement this more permanent Framework document, the Agency envisions a bookshelf concept whereby topical evaluations could be undertaken as supplements to the Framework in order to capture the evolving science and particularly complex topics. Once the Metals Framework is finalized, the Agency can determine whether any particular topics require a more detailed evaluation and/or review. The Agency will refer to the SAB long-term recommendations when determining the nature and extent of follow-up projects supplementing the Framework.

With regard to the SAB's related recommendation that EPA use the term "factors" rather than "principles" to be considered in metals risk assessment, the Agency plans to retain the use of the term "principles" to mean a fundamental truth (or property) of metals that significantly influences how risk assessments should be done. The Agency believes that the use of the term "principle" is important in that the discussed items are fundamental concepts that should be considered in any metals risk analysis in order to ensure technical soundness. In keeping with the SAB recommendations, the Agency plans to expand on the principles originally articulated in the draft Framework in order to amplify and balance the discussion among the different items and more clearly articulate these discussions as principles (rather than factors). The Agency will also consider the SAB recommendation to include other topics, such as the nature and type of metals source, the route of metals exposure, and involvement of metals in biogeochemical cycles.

2. The scientific synthesis in the human health and ecological sections of the Framework is incomplete and in need of major revision. Important scientific issues in other parts of the Framework are either missing or lack clarity. Specific SAB comments and recommendations are provided to address these concerns.

The SAB comments and recommendations are presently being reviewed by a team of expert human health and ecological risk assessors. All of the SAB's comments and recommendations will be carefully considered, and the Framework will be revised to address the Panel's overarching and short-term recommendations. The long-term recommendations will also be considered and acknowledged, as appropriate. Both the human health and the ecological sections of the Framework will be revised to provide a balanced treatment of the scientific issues in accordance with the planned restructuring of the document. These issues will be addressed by considering how the metal-specific principles should be applied in

human health and ecological assessments using various spatial scales and levels of complexity.

EPA agrees with the SAB recommendation that there should not be a distinction in the Framework between the term "bioaccumulation" to describe metal concentrations in aquatic and terrestrial species and "accumulation" of metals in humans. That is, metals can bioaccumulate in aquatic organisms, terrestrial organisms, humans, and other animals. The Agency agrees with the SAB comments that in humans, as in other animals, the steady-state body burden of many metals is under homeostatic control, thereby balancing intake and excretion within certain ranges of metal exposure. Furthermore, the Agency agrees that, for certain metal compounds, bioaccumulation kinetics are slow, which results in a persistent increase in tissue or body burdens over time. This may result in a lag time, so current body or tissue burdens may be correlated with a higher prior exposure (rather than with current exposure levels) and will increase with age. Furthermore, EPA agrees with the SAB's recognition that some metals do bioaccumulate in the tissues of humans to levels that result in toxic effects. The Agency agrees with the SAB-recommended modification of the definition of bioaccumulation to read, "The net accumulation of a metal in a tissue of interest or the whole organism that results from exposure to all environmental sources, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a net balance between uptake and elimination of the metal." The Agency also acknowledges the SAB's concurrence with the draft Framework recommendation that while it is important to consider bioaccumulation as part of an assessment of a metal, use of bioaccumulation factors and bioconcentration factors are not scientifically supported for use as generic threshold criteria for the hazard assessment of metals. As recommended by the SAB, the Agency plans to revise the underlying discussion to clarify the text and eliminate redundancy in light of the recommendations.

The SAB also expressed particular concern about the human health sections of the Framework. The Agency plans to undertake a major revision and update the human health sections, although many of the topics that are discussed in the draft Framework (e.g. essentiality, mixtures, toxicokinetics) will be retained in updated discussions. An area that was a source of confusion in the initial draft Framework centered on the typical starting point of human health risk assessment by Agency risk assessors. Human health risk assessors in the Agency will usually access toxicological data and consensus-established reference values (e.g. reference dose, reference concentration, cancer slope factor) from another source separate from the risk assessment, such as EPA's Integrated Risk Information System or the Agency for Toxic Substances and Disease Registry. Thus, while it is important for the risk assessor to understand the toxicological database, mechanisms of toxicity, hazard assessment, and the derivation of particular reference value(s) – and how these values relate to the unique attributes of metals (e.g. essentiality, recommended daily allowances) – human health risk assessors in the Agency are generally not involved in developing the reference values. The Agency plans to revise the Framework to clarify these aspects of the EPA human health risk assessment process, further clarify metal-specific considerations for exposure assessment, and take these into account in the risk assessment process.

The SAB also pointed out a number of specific issues that need to be addressed. Examples include the treatment of respirable particulate matter, mixtures, dermal exposure, bioavailability, low-dose effects, and interactions between metals and organic chemicals. These and other technical comments from the SAB will all be fully evaluated and considered in a manner appropriate to the plan for restructuring the document in order to address the SAB's first major comment (i.e. the dual nature of the document). To further address SAB comments, the Agency plans to ensure more balance in the discussion of different types of assessments (site-specific vs. national criteria setting) and to clearly define important terms (e.g. speciation).

3. **The Framework provides comprehensive coverage of available tools and methods for metals risk assessment. However, critical evaluations of tools and methods are sometimes unbalanced or lacking. The Framework should focus on the strengths, weaknesses, and limitations of various methods and tools. Where appropriate, comparative assessment of competing approaches should be provided.**

As indicated under Item 1, the Agency plans to revise the Framework to focus on how the unique attributes and principles related to metals can be incorporated into EPA human health and ecological risk assessment guidance and practices. Nonetheless, the Agency is sensitive to the comments from the SAB that some of the Framework evaluations were unbalanced or lacking and plans to carefully focus on ensuring balanced coverage of topics throughout the revised Framework, particularly those topics and issues that span both human health and ecological risk assessment. The revised Framework will include illustrative examples throughout the document, as recommended by the SAB. In instances where tools or methods are incorporated as examples to illustrate a particular principle or concept, the Agency will strive for completeness and a balanced discussion. The general descriptions of the applications and limitations of particular tools and methods will be significantly scaled back in keeping with the revised structure and focus of the Framework.

4. **The Recommendations section of the Framework should be revised to reduce the overall number of recommendations by combining redundancies and eliminating those statements that are not recommendations. Recommendations in the Framework should also be organized according to their specificity (i.e. from general overarching to more specific), and each recommendation should be adequately supported by text and references as appropriate.**

The Agency agrees with this recommendation from the SAB and, as the revised Framework is restructured, the number of recommendations is expected to be significantly reduced. Those recommendations that remain will be focused on metal-specific attributes and principles in risk assessment. In addition, the Agency plans to eliminate the redundancy of some of the recommendations, as suggested by the SAB, and will ensure appropriate textual support and referencing.

In conclusion, the Agency appreciates the many thoughtful and constructive suggestions provided by the SAB on this important document. We are carefully considering

all of the SAB's comments and recommendations and believe that the review panel's input will result in a Metals Framework that is greatly improved and of long-term value to EPA risk assessors.