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

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

January 25, 2006

EPA-SAB-06-002

The Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Review of EPA's Draft Framework for Inorganic Metals Risk Assessment

Dear Administrator Johnson:

The Environmental Protection Agency's Office of Research and Development requested that the Science Advisory Board (SAB) review the Agency's draft *Framework for Inorganic Metals Risk Assessment* (the Framework). The Framework was developed to supplement previous EPA guidance for risk assessment activities related to metals. A panel of the SAB reviewed the Framework and has commented on the state of the science presented in the document, as well as the recommendations, supporting tools, methods, and models. The enclosed SAB report addresses EPA's charge questions to the Panel and provides recommendations to improve the Framework.

The SAB commends EPA for initiating the development of a comprehensive risk assessment framework for metals and metalloids. The SAB finds that the Framework covers the main areas of concern to risk assessors. However, the SAB also finds that technical corrections and additions are needed and that the document should be restructured and substantially revised to improve the clarity of expression, precision of wording, and balance and depth of coverage of important topics. In this regard, the SAB finds that:

- 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*.

- 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 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.

- 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.

In summary, the SAB finds that the Framework for Inorganic Metals Risk Assessment is an important document that will guide EPA and others in evaluating metals in ecological and human health risk assessment. Revision of the Framework is necessary before it is published in final form in order to make it of more current and long-term value to EPA. The SAB strongly urges EPA to continue developing the Framework and has provided specific comments and recommendations to improve the document. The SAB is willing to provide additional review of the revision of the Framework.

Sincerely,

/signed/

Dr. M. Granger Morgan, Chair
EPA Science Advisory Board

/signed/

Dr. Deborah L. Swackhamer, Chair
Metals Risk Assessment
Framework Review Panel
EPA Science Advisory Board

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U.S. Environmental Protection Agency
Science Advisory Board
Metals Risk Assessment Framework Review Panel

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1. EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) Science Advisory Board (SAB) Metals Risk Assessment Framework Review Panel has reviewed EPA's draft *Framework for Inorganic Metals Risk Assessment* (the Framework). This report transmits the SAB's comments and recommendations. Many EPA programs face decisions on whether and how to regulate metals. These decisions range from setting standards or permits for environmental releases to establishing safe levels in different environmental media, to setting priorities for programmatic or voluntary efforts. EPA developed the draft *Framework for Inorganic Metals Risk Assessment* to supplement previous Agency guidance for use in site-specific risk assessments, criteria derivation, and other similar Agency activities related to metals.

EPA followed a stepwise process to develop the Framework document. A Metals Action Plan was first developed to provide brief descriptions of EPA's current activities related to metals and to identify critical scientific issues to be addressed. After the Metals Action Plan was reviewed by the Science Advisory Board, issue papers were developed to discuss key scientific topics pertaining to inorganic metals. The draft document, *Framework for Inorganic Metals Risk Assessment* was then completed and submitted to the SAB for review. The Framework document contains five sections: 1) an introduction describing the purpose, audience, and scope of the document; 2) a problem formulation section setting forth principles of metals risk assessment and providing a conceptual model for metals assessments; 3) a section providing recommendations that should be considered when conducting assessments of the ecological or human health risks associated with metals exposures; 4) a section on metal specific topics and methods in environmental chemistry, human health exposure pathway analysis, human health effects, ecological exposure pathway analysis, and characterization of ecological effects; and 5) a section identifying metals research needs.

EPA sought comment from the SAB on the scientific soundness of the Framework's synthesis and representation of the state of the science. Specifically, EPA sought comment on the overall objectivity and utility of the recommendations and supporting tools, methods, and models to its primary audiences (EPA risk assessors and the public), and whether there were any additional research needs that warrant inclusion or further discussion in the Framework. EPA defined objectivity as: "a focus on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased." EPA defined utility as: "the usefulness of the information to its intended users, including the public."

The SAB notes that the Framework will be an important document. It will be used by EPA to develop more detailed risk assessment guidance, and it will be used by both EPA and the external community as an authoritative compilation of the state of science regarding metals in the environment. The SAB commends EPA for initiating the development of a risk assessment framework for metals that covers a broad spectrum of topics related to human health and ecological risk concerns associated with exposure to toxic metals and metalloids. The SAB finds that the Framework clearly identifies the unique attributes of managing metals. However, the SAB also finds that a number of major issues within the Framework document need to be addressed. In order to make the Framework of long-term value to EPA, significant revision of

the document is required before it is published in final form. The SAB notes that the overall clarity of expression, precision of wording, and balance in coverage among topics in the Framework must be greatly improved. In response to EPA's charge questions, the SAB provides specific comments and recommendations for improvements in the Framework. In addition, the SAB has noted other recommendations for improvement that are overarching in scope and not related to specific charge questions. Because of the scope of revisions recommended, the SAB believes the revised Framework would benefit from a second external peer review. The SAB is willing to provide such a review.

Overall Framework Scope (Charge question 1.1)

- The SAB generally finds that the overall Framework scope is sufficiently broad and provides an appropriate level of flexibility in addressing issues of concern. The SAB supports the idea of treating both human health and ecological risks in one document in order to consistently present risk assessment concepts. However, a major weakness in the current version of the Framework is the lack of consistency in identity. The Framework appears to vacillate between being a description of basic principles to a methods manual. The SAB therefore recommends that the Framework be reviewed and revised to remove any confusion in its intended purpose. If the document is to serve as both a framework and a practical guide for risk assessors, the recommendations and guidance in the document should be balanced and organized consistently with this dual purpose in mind. The SAB recommends that EPA clearly identify and carefully differentiate material that is presented as "the framework for assessment," "examples to illustrate and clarify framework issues," and "specific instructions."

General Risk Assessment Categories in the Framework (Charge question 1.2)

- The SAB generally finds that the risk assessment categories listed in the introduction of the Framework are an appropriate context to cast the relevant issues of metals in comparison to organic compounds. However the SAB recommends that the scope of the assessment categories be more clearly defined, and that the number of assessment categories be expanded to span the range of complexity among screening and site-specific risk assessments conducted at different scales. The SAB also finds that the sections of the Framework following the introduction largely concern site-specific assessment issues. The SAB recommends that the subsequent sections of the document be revised to represent more balance among the different types of assessments.

Articulation/Objectivity of Metals Assessment Principles (Charge question 2.1)

- The SAB notes that the framework discusses factors to be considered in metals risk assessment rather than principles. The SAB therefore recommends that EPA use the words "factors to be considered" or "factors" in Section 2 of the Framework instead of "principles." The SAB finds that there is an imbalance in coverage of factors in the Framework and recommends inclusion in the document of a number of important factors such as nature and type of metals source, route of metals exposure, and involvement of metals in biogeochemical cycles. The SAB also recommends that EPA list key questions

for all of the factors discussed in the Framework. The discussion associated with the key questions should identify why the factors are uniquely important for metals risk assessment.

Conceptual Model (Charge question 2.2)

- The SAB finds that the conceptual model in the Framework is sufficiently comprehensive. However the SAB recommends that the model be revised to emphasize a number of key concepts discussed in the response to charge question 2.2 below, and to more clearly distinguish differences between metal/metalloid and organic pollutants. The SAB also recommends that the conceptual model be more clearly linked to the related discussion in various parts of the Framework.

Recommendations in the Framework (Charge question 3.1)

- The SAB has identified revisions needed to address technical issues concerning the recommendations section of the Framework (Section 3). Specific revisions are suggested in the response to charge question 3.1 below. The SAB finds that the clarity of the framework could be improved by organizing the recommendations according to their specificity (i.e., from the most critical general overarching recommendations with the greatest impact to more specific recommendations of interest to the assessor). The SAB recommends that the Framework be revised to reduce the number of recommendations in the document by combining those that are redundant or similar. It is also recommended that prescriptive recommendations be generalized or cited as examples of appropriate applications of metals principles. EPA should also review the Framework and make necessary revisions to ensure that the recommendations are expressed as recommendations, not simply factual statements.

Objectivity and Utility of the Data, Tools, and Methods in Section 4 of the Framework (Charge question 3.2)

- The SAB finds that the human exposure and health effects discussion in Section 4 of the Framework is incomplete and in need of major revision. For example, the Framework is incomplete in the following areas:

    1. Treatment of particulate matter. Particulate matter less than 2.5 micrometers in size and nanoparticles are of critical concern for the exposure and delivery of metals to humans and this is ignored in the Framework.

    2. Characteristics of inhaled particles. The characteristics of inhaled particles are critical determinants of metals uptake in humans and this is not addressed in the Framework.

    3. Inhaled mixtures. Biological effects of inhaled mixtures such as metals in combination with other airborne pollutants are not addressed in the Framework.

4. Dermal exposure and uptake of metals. Dermal exposure and uptake of metals are not adequately addressed in the Framework.

5. Effects of metals at low doses. The Framework does not provide a discussion of the toxic effects of metals at low doses.

6. Interactions between metals and organic chemicals. There is insufficient discussion in the Framework of the interactions between metals and organic chemicals and how these interactions can lead to potentiation or antagonism.

The SAB recognizes that a rewrite addressing areas of incompleteness may not be achievable in the short-term, but it will be essential if the treatment of human exposure and health effects is to be of equal value and quality to other parts of the Framework. Recommendations to improve the human exposure and health effects discussion are provided in the responses to charge question 3.2 and in the detailed comments in Appendices A and C.

- The SAB finds that the environmental chemistry discussion in Section 4 of the Framework is comprehensive, but in many instances critical evaluations of the tools and methods are not provided, and the justification for many recommendations is not clear. As discussed below, the SAB recommends that more emphasis be placed on developing comparative assessments of available tools and methods.

- The SAB finds that the ecological exposure and effects discussion in Section 4 of the Framework provides a great deal of supporting information for the recommendations articulated in the document. However, the treatment of various topics addressed in the ecological exposure and effects section is uneven and leaves the impression of not being objective. In some places, the discussion does not fully reflect the state of the science. The SAB recommends that the bioaccumulation and bioavailability sections of the Framework treat the routes of exposure (diet and dissolved metals) in an integrated fashion. This could be accomplished by organizing the discussion around the bioavailability conceptual model. The SAB recommends that the toxicity testing section of the Framework discuss uncertainties, such as the lack of dietary exposure in laboratory toxicity tests, that are of particular importance to metals risk assessment. The SAB recommends that the discussions of sediment contamination be revised to address important principles and methods that are currently absent. The SAB also recommends that the discussion of simultaneously extracted metals-acid volatile sulfides (SEM-AVS) be revised to capture the controversies surrounding this approach. In addition, the discussion of the biotic ligand model (BLM) should address the limits of the approach and its early state of development.

Metals Speciation (Charge question 3.3)

- The SAB commends EPA for emphasizing the concept of metals speciation in the Framework. However, the SAB finds that a clear definition of the terms species and speciation should be included in Section 2 of the document. The SAB provides such

definitions in Appendix B of this report. As discussed in the response to charge question 3.3 below, the SAB also finds that the treatment of speciation in the Framework could be improved by providing more accurate and detailed information. The SAB finds that the value of some approaches to considering speciation is overstated in the Framework (e.g., application of the biotic ligand model to chronic or natural exposures). Other approaches to considering speciation are ignored in the Framework (e.g., direct measurement of speciation). The SAB recommends that appropriate linkages between speciation and the concepts used in risk analysis, such as partitioning and bioavailability, be emphasized in the Framework. In addition, it would be helpful to include a fuller description of the currently available tools to quantify metal speciation in environmental samples, including the strengths and weaknesses of each technique. The SAB notes that the paucity of data to support modeling of speciation limits the risk assessor's ability to include speciation in metal risk assessment tasks at site and national scales. However, because of transformations that occur as metals cycle through the environment, metal speciation determination is more applicable for site-specific investigations than the setting of national standards.

Summary Recommendations Tables in the Framework (Charge question 3.4)

- The SAB finds that summary recommendation tables such as example Table A-1 in the Framework can be used to effectively present important recommendations in an organized manner. As discussed in the response to charge question 3.4, the SAB recommends that the tables be restructured to relate the recommendations to the categories of risk assessment discussed in the document.

Environmental Chemistry (Charge questions 3.5 – 3.7)

- *Objectivity of Hard Soft Acid Base Concept*. The SAB finds that the application of the Hard Soft Acid Base concept to the stability of metal complexes in the general context of risk assessment is presented in an unbiased manner. However, the SAB recommends that general statements in the Framework indicating that hard acids are more toxic than soft acids should be worded more carefully. The SAB notes that the Hard Soft Acid Base concept is useful for assessing the relative strength of binding of a metal to a receptor, but the toxic response to bound metal is not adequately addressed by the Hard Soft Acid Base concept.

- *Objectivity of Atmospheric Metal Chemistry Discussion.* The SAB notes that none of the Metals Risk Assessment Framework Review Panel members has an active research program in atmospheric chemistry. The SAB therefore recommends that an atmospheric chemist review the atmospheric chemistry sections of the Framework to ensure that there are no gaps in coverage beyond those identified in the response to charge question 3.6.

- *Objectivity of the Chemistry and Environmental Parameters in Metal Surface Complexation and Partition Coefficient Models.* The SAB finds the Framework discussion of surface complexation models to be generally accurate and unbiased. However, in response to charge question 3.7 below the SAB identified a number of areas

where the presentation lacks completeness. The SAB has provided recommendations to improve these sections of the document.

Human Exposures and Effects (Charge questions 3.8 – 3.10)

- *Objectivity of the Discussion on Natural Background of Metals.* The SAB recommends that EPA use the term "ambient" or "ambient levels" in the Framework rather than "background." The SAB also recommends defining and using the terms "body burden" and "human biological monitoring" in the Framework glossary and text. The SAB finds that the term "background" is often incorrectly assumed to connote natural and therefore safe, or of no significant human or ecological health concern. However, ambient levels can vary, or can be inherently high enough to represent a potential health concern by themselves. Ambient levels can also represent a total concentration from a combination of natural and anthropogenic sources, some of which may be historical or unknown. The SAB acknowledges, however, that the term "background" exposure has been used in human health dose response assessment. This term, referring to both the natural and anthropogenic sources of a chemical under assessment, has been used in various publications on dose-response modeling over the past 25 years or more.

- *Objectivity of the Discussion of Essentiality Versus Toxicity*. The SAB finds that revisions are needed in the Framework to clarify and ensure accuracy of the discussion of essentiality versus toxicity. The SAB recommends that EPA carefully define "essentiality," recognize that metals essential to some organisms may not be essential to others, recognize that essential metals can cause adverse health effects at elevated concentrations, and recognize that the source and route of exposure play an important role in the toxicity of essential metals.

- *Objectivity of the Discussion and Recommendations for Assessing the Toxicity of Mixtures.* The SAB finds that the Framework requires revision to more explicitly address a number of issues concerning metals mixtures. The SAB recommends that the Framework be revised to address: competitive interactions among chemically similar metals/metalloids (mimicry), reduction of metal reactivity and increase in mobility by organic compounds that form complexes with metals, and possible increases in toxic effects for organic compounds that form lipophilic complexes with metals.

Ecological Exposures and Effects (Charge questions 3.11-3.14)

- *Objectivity of the Discussion and Recommendations Concerning Natural Background, Bioavailability, Bioaccumulation, Biomagnification, and Trophic Transfer*. The SAB finds that the Framework discussions of natural background, bioavailability, bioaccumulation, biomagnification, and trophic transfer require revision to address inconsistencies between Sections 3 and 4 of the document. In the response to the charge question 3.11, the SAB recommends specific revisions to integrate the sections, address imbalance among the recommendations, integrate discussions of uncertainties, and address omissions.

- *Objectivity of the Framework Discussion Concerning the use of Bioconcentration factor (BCF) and Bioaccumulation Factor (BAF).* The SAB agrees with the statement in the Framework indicating that BCF/BAF methodologies are not good measures of hazard for metals. However, the SAB finds that a clearer and more systematic discussion is needed in the document to justify this statement. The SAB recommends that EPA revise the Framework to include a discussion of what could replace BCF/BAF as a measure of bioaccumulative potential and where BCF/BAF approaches are useful.

- *Derivation of Bioaccumulation Factors (BAFs) and Bioconcentration Factors (BCFs).* The SAB finds that the mathematical relationships in the Framework appropriately represent the metals concentration in the organism or tissue as a function of the bioavailable concentration in the exposure medium/media for each set of exposure conditions. However, the SAB recommends that in the future, EPA incorporate a bioenergetics approach into the Framework. Such an approach offers valuable potential for understanding metal accumulation from air, sediments, soils, or water. In the interim, the SAB recommends that the Framework address metals bioaccumulation empirically for site assessments.

- *Objectivity of Information and Recommendations Concerning use of Simultaneously Extracted Metal-Acid Volatile Sulfides (SEM-AVS) Approach and the Biotic Ligand Model (BLM).* The SAB finds that the Framework comprehensively describes the theory and evidence supporting the use of the SEM-AVS approach and the BLM. However, as further discussed in the response to charge question 3.14 below, the SAB finds that the Framework is unbalanced in presenting the practical and theoretical challenges and inherent limitations encountered in the use of these methods. The SAB recommends that the Framework be revised to provide a more balanced presentation of the "pros and cons" associated with the methods.

Additional Major Revisions

- *Title.* The SAB finds that the title of the Framework is awkward: metals are inorganic by definition, and thus the use of the adjective "inorganic" in front of metals is redundant. Although the SAB realizes that the adjective "inorganic" was probably used in the original title to exclude organometallics, especially methylmercury, it detracts from the clarity of the title. A better title would be "Framework for Assessment of Risk of Metals and Metalloids in the Environment." At the beginning of the Framework document, EPA should clarify the rationale for specifically excluding organometallic compounds from the document while including natural transformation pathways that form organometallic compounds.

- *Balance and Comparability Among Sections.* The SAB finds that Section 3 of the Framework should be reorganized and rewritten to provide more comparability among the discussions of human health effects, aquatic effects, and terrestrial effects. The SAB recommends that the aquatic section be modeled on the terrestrial section. Recommendations should be highlighted by cross-referencing justification to Section 4 of the Framework and minimizing textual justification.

- *Restructuring of Framework Document*. The SAB recommends that Section 4 of the Framework be reorganized to mirror the organizational structure used in Section 3.

- *Illustrative Examples.* The SAB finds that illustrative examples would be useful throughout the document. Examples of how certain recommendations might be implemented would greatly improve the utility of the document.

- *Discussion of Uncertainties and Data Quality*. The SAB finds that the discussion of uncertainties of tools, methods and data is generally lacking and inconsistent throughout the Framework. The SAB recommends that the importance of critically considering data quality be explicitly stated throughout the document wherever the use of analytical data is discussed.

- *Use of the term "Bioaccumulation" versus "Accumulation" to Describe Metals Concentrations*. It is the opinion of the SAB that there should not be a distinction in the Framework between the term "bioaccumulation" to describe metal concentration in aquatic and terrestrial organisms and the term "accumulation" of metals for humans. This is not an accepted distinction in the scientific community. In humans as in other terrestrial animals, the steady-state body burden of many metals is under homeostatic control that balances intake and excretion. However, for certain metal compounds bioaccumulation can occur, which can be defined as either a persistent increase in individual steady-state levels that is correlated with higher prior exposure, and/or a progressive increase in body burden as a function of exposure time or age, that is above normal steady-state levels and which may involve selective bioaccumulation of the metal in certain tissues. The SAB believes it is important to recognize that some metals do bioaccumulate in the tissues of humans and that this bioaccumulation is related to their toxicity. To clarify what is meant by bioaccumulation, the SAB recommends that the definition of the term "bioaccumulation" in the glossary of this document be modified to read as follows:

  Bioaccumulation: 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 mass balance between uptake and elimination of the metal.*

- *Metal-specific Reference Values (RfD/RfC) and/or Cancer Potency Factors*. The SAB recommends that, in introducing the Human Health Effects Section, EPA set the context by explaining that human health risk assessors start their analysis with a metal-specific reference value (RfD/RfC) and/or cancer potency factor that has been developed through a process separate from the risk assessment. The role of the human risk assessor is to appropriately integrate the reference values and potency factors with the exposure assessment. Thus, the risk assessor needs an understanding of the toxicological endpoints and mechanisms of action that underlie the derivation of these values to ensure that, for example, the appropriate population and life stages are addressed, appropriate dietary aspects are taken into consideration, and the appropriate exposure pathways are

considered. For metals, frequency and duration of exposure, as well as exposure concentrations, are important parameters to be considered for accurate dose assessments. The Framework should focus on advising human health risk assessors on how to take these considerations into account in constructing the risk assessment.

- *Modeling*. The SAB notes that the Framework accurately reflects the fact that modeling the environmental fate and transport of metals differs in significant ways from modeling organic compounds. However, descriptions of a number of models are included in the Framework with little or no information presented on requirements for:1) adapting existing models for metals applications, 2) developing new metals-specific models for risk assessment, 3) establishing data requirements for model calibration, or 4) determining suitable techniques for estimating parameter values (and associated uncertainties). The SAB finds that further guidance will need to be developed in this area.

- *Removing Section on Metal Research Needs*. The SAB feels strongly that the identification of research needs should not be within the scope of the current Framework. The SAB notes that in the Framework there has not been a thorough review of all research areas and it is not appropriate in the given context to highlight and identify specific research needs for the future. Therefore, the SAB recommends that the research needs section (Section 5) of the Framework be removed. A separate, follow-up document identifying and prioritizing research needs would be helpful if it were done in a comprehensive manner. The Framework could refer to this separate document. Research recommendations provided by the SAB in this report could be included in the separate research needs document.

While these recommendations call for substantial revision of the Framework, the SAB commends EPA for initiating the development of a much-needed risk assessment framework for toxic metals and metalloids and strongly urges EPA to continue developing the document. The SAB provides specific comments and recommendations to improve the Framework. Given the large number of recommendations, the SAB identified those that could be completed in the "short-term" (i.e., within six months), and those that require a more "long-term" effort. This determination is based on the subjective judgment of the SAB. The next version of the Framework is not expected to fully address the long-term recommendations but should acknowledge them.

Review of EPA's Draft Framework for Inorganic Metals Risk Assessment

A Report by the Science Advisory Board Metals Risk Assessment Framework Review Panel

2. INTRODUCTION

The U.S. Environmental Protection Agency (EPA) Science Advisory Board (SAB) Metals Risk Assessment Framework Review Panel has reviewed EPA's draft document *Framework for Inorganic Metals Risk Assessment* (Framework). This report transmits the SAB's comments and recommendations. Many EPA programs face decisions on whether and how to regulate metals. These decisions range from setting standards or permits for environmental releases, to establishing safe levels in different environmental media, to setting priorities for programmatic or voluntary efforts. EPA developed the draft *Framework for Inorganic Metals Risk Assessment* to supplement previous Agency guidance for use in site-specific risk assessments, criteria derivation, and other similar Agency activities related to metals.

EPA has followed a stepwise process to develop the draft Framework. A Metals Action Plan (MAP) was first developed to establish a process for application of scientific principles to metals risk assessment. In September 2002, the SAB reviewed the MAP and provided comments to EPA (U.S. EPA SAB, 2002). EPA then developed metals issue papers addressing the following topics: environmental chemistry of metals, biovailability and bioaccumulation of metals, metal exposure assessment, human health effects, and ecological effects (U.S. EPA, 2004). The draft Framework document was then completed, and a peer consultation workshop was held in July 2004 to seek input on the document from scientists in the field of metals risk assessment. The Framework document was then revised and provided to the SAB for review. The draft Framework document contains five sections: 1) an introduction describing the purpose, audience, and scope of the document; 2) a problem formulation section setting forth principles of metals risk assessment and providing a conceptual model for metals assessments; 3) a section providing recommendations that should be considered when conducting assessments of the ecological or human health risks associated with metals exposures; 4) a section on metal specific topics and methods in environmental chemistry, human health exposure pathway analysis, human health effects, ecological exposure pathway analysis, and characterization of ecological effects; and 5) a section identifying metals research needs.

The SAB commends EPA for recognizing the need to carefully analyze the differences between metals and organic chemicals in site specific and national risk assessments. Specifically, the SAB congratulates EPA for initiating the development of a risk assessment framework for metals that covers a broad spectrum of topics related to human health and ecological risk concerns from exposure to toxic metals and metalloids. The SAB's comments are directed to the EPA to help develop a strong final document that will help guide Agency risk assessors for a number of years into the future.

3. CHARGE TO THE REVIEW PANEL

EPA sought comment from the SAB on the scientific soundness of the Framework's synthesis and representation of the state of the science. Specifically, EPA sought comment on: the overall objectivity and utility of the recommendations and supporting tools, methods, and models to its primary audience (EPA risk assessors and the public), and whether there are any additional research needs that warrant inclusion or further discussion in the Framework. EPA defined objectivity as: "a focus on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased." EPA defined utility as: "the usefulness of the information to its intended users, including the public." The EPA gave the following eighteen charge questions to the SAB panel.

Question 1: Section 1 - Framework Scope and Assessment Categories

1.1 Please comment on the overall framework scope and whether it is sufficiently encompassing to allow for the consideration of the broad spectrum of physical and chemical properties, exposures, and effects among inorganic metals and metal compounds.

1.2 The context of the regulatory application (e.g., contaminated site clean-up, national regulation, or programmatic decision) is a major factor in determining the type of analysis that is appropriate for a particular assessment. The framework identifies three general categories of assessments, including site-specific assessments, national scale assessments, and national ranking and categorization. With the understanding that screening and detailed assessments occur within the assessment categories, please comment on the utility of these categories in setting the context for discussion of metals assessment.

Question 2: Section 2 - Problem Formulation, Metals Principles, and Conceptual Model

2.1 Please comment on whether the discussion of inorganic metals assessment principles is clearly articulated, objective, as defined above, and has utility.

2.2 Please comment on how well the conceptual model presents key metal processes and whether (or not) it is complete.

Question 3: Sections 3, 4, and 5 – Recommendations, Tools/Methods, and Research Needs

3.1 Please comment on how well the recommendations under Section 3 are supported by the detailed information in Section 4. Are there other recommendations that should be included? Are there any inorganic metals or metal compounds for which any of the recommendations would not apply?

Note: Recommendations pertaining to environmental chemistry are distributed throughout Section 3, particularly under Sections 3.2.1 and 3.3.1 presenting recommendations on environmental fate and transport.

3.2 Please comment on the objectivity and utility of the data, tools, and methods discussed in Section 4. Identify any scientific or technical inaccuracies, or any emerging areas or innovative applications of current knowledge that may have been overlooked or warrant a better discussion of uncertainty, including areas needing further research.

3.3 Please comment on the state of the science (i.e., data, tools and methods) to address inorganic metals speciation in all environmental compartments for any given inorganic metal from the point of environmental release to the point of toxic activity as discussed in the document. Please comment on whether the framework identifies appropriate research needs to overcome any limitations in the state of the science. Please address these questions separately for each of the three types of assessments presented (i.e., site-specific, national level, and ranking and categorization.)

3.4. In an earlier draft of the framework, EPA had included three Summary Recommendation Tables in Section 3 on human health, aquatic, and terrestrial risk assessment, covering the three general assessment categories (i.e., site-specific, national level, and ranking and categorization). An example of this table is included as Appendix A in the draft provided to the SAB. To minimize confusion for users of the framework, the initial idea behind the recommendations and adjoining table was to have concise recommendations on the science, followed by a separate accounting of how these recommendations could then be applied to the different assessment categories. Reviews have been mixed on the utility of these tables as a sufficient communication tool. Please comment on whether tables of this type would be useful for inclusion in the final version of the framework. Does the panel have alternative suggestions for effectively communicating how the recommendations can be considered for each of the three assessment levels?

Environmental Chemistry (Sections 3.3.1, 4.1)

3.5 Please comment on the objectivity of the Hard Soft Acid Base concept to applications of stability of metal complexes in toxicity assessments. See Section 4.1.2.

3.6 Please comment on the objectivity of the atmospheric metal chemistry discussion and its application to exposure assessments. See Sections 3.3.1.1 and 4.1.7.

3.7 Please comment on the objectivity of the metal chemistry and environmental parameters incorporated in the various metal surface complexation and partition coefficient models and their applications to exposure assessments. See Sections 3.3.1.2 and 4.1.4.1.

Human Exposure and Health Effects (Sections 3.1, 4.2, 4.3)

3.8 Please comment on the objectivity of the discussion and recommendations on natural background of metals. See Sections 3.1.2.1 and 4.2.2.1.

3.9 Please comment on the objectivity of the discussion of essentiality versus toxicity, including the relationship between Recommended Daily Intakes (RDAs) and thresholds such as Reference Doses (RfDs) and Reference Concentrations (RfCs). See Sections 3.1, 4.3.2, and 4.3.3.

3.10 Please comment on the objectivity of the discussion and recommendations presented for assessing toxicity of mixtures, including how to assess additivity versus departure from additivity. See Sections 3.1.3.4 and 4.3.6.

Ecological Exposure and Effects (Sections 3.2, 3.3, 4.4, 4.5)

3.11 Please comment on the objectivity of the discussion and recommendations concerning natural background, bioavailability, bioaccumulation, biomagnification, and trophic transfer in both aquatic and terrestrial environments. See Sections 3.2.2 to 3.2.4, 3.3.2, 4.4.3, 4.5.4, and 4.5.6 to 4.5.9.

3.12 Please comment on the objectivity of the framework statement that the latest scientific data on bioaccumulation do not currently support the use of bioconcentration factor (BCF) and bioaccumulation factor (BAF) values as generic threshold criteria for hazard classification of inorganic metals (see recommendation on page 3-17, lines 27-29 of the document). By this, the framework means that various assumptions underlying the BCF/BAF approach, including the independence of BCF/BAF with exposure concentration and the proportionality of hazard with increasing BCF/BAF do not hold true for the vast majority of inorganic metals assessed. Please comment on the framework's acknowledgement that the appropriate use of BCFs/BAFs to evaluate metal bioaccumulation, including the degree to which BCFs/BAFs are dependent on exposure concentrations, needs to consider information on bioaccessibility, bioavailability, essentiality, acclimation/adaptation, regulation of metals (uptake and internal distribution), detoxification and storage, dependence on exposure concentration, and background accumulation. While the ability to quantitatively address all these factors may be limited at the present time, the framework states that their potential impacts should at least be qualitatively addressed. See Sections 3.2.4, 3.3.2.5, and 4.5.8.

3.13 Given the variety of organism responses to inorganic metals exposure, based on factors such as bioaccessibility, bioavailability, essentiality, uptake/excretion mechanisms, and internal storage/regulation, as described in Section 3.2.4, the framework states that BAFs/BCFs should be derived using mathematical relationships that represent the concentration in the organism or tissue as a function of the bioavailable concentration in the exposure medium/media for each set of exposure conditions. Please comment on whether this is the best approach based on the current state of the science or if there are alternative approaches that are more appropriate that can be routinely applied. See Sections 3.2.4, 3.3.2.5, and 4.5.8.

3.14 Please comment on the objectivity of the information and recommendations pertaining to the use of the simultaneously extracted metals-acid volatile sulfides (SEM-AVS) approach and the biotic ligand (BLM) model. Are additional recommendations warranted? If yes, what are they? See Sections 3.2.6, 4.4.2.3, and 4.5.10.

4. REVIEW PROCESS

To establish the Metals Risk Assessment Framework Review Panel, the EPA Science Advisory Board Staff Office published a Federal Register notice requesting nominations and

identified a subset of nominees for consideration as panelists. The final panel was selected after requesting public comments on the nominees and further evaluating them against EPA Science Advisory Board selection criteria. The members of the review panel included scientists with expertise in: the environmental chemistry of metals, environmental fate and transport of metals, bioavailability of metals, routes of exposure of aquatic and terrestrial species to metals, routes of human exposure to metals, human health effects of exposure to metals, and ecological effects of exposure to metals.

The SAB review was conducted by a public teleconference and a two and one half day public face-to-face meeting of the SAB Panel. During the public conference call, EPA answered questions from the Panel about the draft Framework and the review charge. At the public meeting, the Panel heard presentations from EPA on the Framework and deliberated on the charge questions. The Panel met in the following three working groups to develop responses to the charge questions: 1) Environmental Chemistry/Fate and Transport, 2) Human Exposure and Health Effects, and 3) Ecological Exposure and Effects/Bioaccumulation. Responses of the three working groups were integrated by the Panel to develop the final SAB report.

5. OVERARCHING COMMENTS AND RECOMMENDATIONS

The SAB provides a number of broad overarching comments and recommendations to improve the Framework. The SAB notes that the draft Framework is an ambitious attempt to survey the major issues involved in the assessment of human health and ecological effects of metals and metalloids. In this regard, the SAB believes that the following major issues within the Framework document need to be addressed before the document is published in final form in order to make it of more current and long-term value to EPA.

The SAB recommends substantial revision of the Framework to reorganize the document, include additions and corrections, and remove redundancies as detailed in the responses to the charge questions below. Because of the scope of recommended revisions, the SAB believes the revised Framework would benefit from a second external peer review. The SAB is willing to provide such a review. As discussed below, the SAB finds the Human Health section of the Framework, in particular, to be incomplete and in need of major revision. Some critical references are missing, a number of the references cited in Section 4 are outdated, and more recent references should be included. The ecological subsections of the Framework should more fully reflect the state of the science (i.e., they leave the perception of not being objective). The bioaccumulation and bioavailability sections need to treat the routes of exposure (diet and dissolved metals) in an integrated fashion. This could be accomplished by organizing the discussion around the bioavailability conceptual model. The toxicity testing section needs to discuss uncertainties of particular importance to metals: the lack of dietary exposure of test animals to metals in laboratory toxicity tests is a good example. The discussion of simultaneously extracted metals-acid volatile sulfides (SEM-AVS) does not adequately address the limitations of the approach (e.g., bioavailability from oxidized sediments). As noted in the SAB review of EPA's *Integrated Approach to Metals Assessment in Surface Waters and Sediments*, SEM-AVS is of little use in oxidized environments or those where sediments are periodically resuspended (EPA SAB, 2000a). Similarly, discussions of the biotic ligand model (BLM) do not adequately describe its limitations or the early stage of BLM development.

Finally, other approaches such as the National Oceanic and Atmospheric Administration's (NOAA) empirically-derived effects range median (ERM) and effects range low (ERL) approach (Long & Morgan, 1990; 1991) should be included in the discussions.

The following overarching comments and recommendations are discussed in more detail in the responses to the charge questions below.

Presentation

The SAB finds that the overall clarity of expression, precision of wording, and balance in coverage among topics in the Framework must be greatly improved. Many of the SAB's comments below focus on the main technical issues that need to be addressed specifically. However, the SAB finds that sections of the current Framework are unclear and disorganized and that revision is needed to develop a document that is of high quality.

Title

The title of the Framework is awkward: metals are inorganic by definition, and thus the use of the adjective "inorganic" in front of metals is redundant. Although the SAB realizes that the adjective "inorganic" was probably used in the original title to exclude organometallics, especially methylmercury, it detracts from the clarity of the title. A better title would be "Framework for Assessment of Risk of Metals and Metalloids in the Environment." At the beginning of the Framework document, EPA should clarify the rationale for specifically excluding organometallic compounds from the document while including natural transformation pathways that form organometallic compounds.

Purpose

The SAB finds that a major weakness in the current version of the Framework is the lack of consistency in identity. At times, the Framework provides background information on the state of the science and general recommendations of "basic principles" that need to be considered for risk assessments of metals. At other times, the report appears to serve as a practical guide for risk assessors, offering specific recommendations of methods and tools (often with insufficient justification for the specific selection). This dual nature of the report stems largely from its intended purpose (as stated on pages 1-1 and 1-2) to serve as a "statement of policy" while at the same time "provide recommendations and foster consistent application" across EPA. The SAB recommends that the purpose of the Framework be reviewed and that the document be revised accordingly to remove any confusion in its intended purpose. If the document is to serve as both a framework and practical guide for risk assessors, the recommendations and guidance in the document should be balanced and organized consistently with this dual purpose in mind. EPA should carefully differentiate material that is presented as "the framework for assessment," "examples to illustrate and clarify framework issues," and "specific instructions." In addition, all recommendations in the Framework should be carefully reviewed and revised to ensure that they are consistent with its intended purpose. As such, the recommendations should focus on the key issues that need to be considered in metals evaluations. Specific methods and tools should be cited accordingly to highlight the current state of the science and to serve as examples. EPA,

however, should refrain from making final recommendations of specific methods and tools until a full evaluation of the strengths and weaknesses of each method and tool is performed.

Critical Evaluation of Supporting Information

The SAB commends EPA for providing fairly comprehensive coverage of available tools for risk assessment and methods for metals analyses. In many instances however, critical evaluations of the tools and methods are not provided and the justification for many recommendations is not clear. The SAB therefore recommends that more information be presented on the strengths, weaknesses, and limitations of the various methods and tools. Where appropriate, comparative assessment of competing approaches should be provided.

Tiered Recommendations in the Framework

The SAB recommends that the recommendations in the Framework be tiered, with the most critical general overarching recommendations (those with the greatest impact) presented first, followed by specific recommendations that would be of value to the assessor. This would help focus the different sections of the Framework to ensure that the most important issues are addressed.

Illustrative Examples

Illustrative examples would be useful throughout the document. Examples of how certain recommendations might be implemented would greatly improve the utility of the document. Identification of important metal sources such as accumulation from coal mining, chromium from plating facilities, silver from photographic facilities and atmospheric deposition of mercury to watersheds might provide an indication of the diverse range of sources that should be examined.

Discussion of Uncertainties and Data Quality

Discussions of uncertainties of the tools, methods and data are generally lacking and inconsistent throughout the document. Data quality is a large concern for metals, particularly measurement of dissolved metals. Historic data must be considered with a critical eye, as the data were often generated before clean-room and trace-level measurement techniques were adopted. The need to critically consider data quality should be explicitly stated throughout the document wherever the use of analytical data is discussed.

Terminology and Additions to the Glossary

As discussed in the detailed responses to the charge questions, and in the recommendation concerning the definition of bioaccumulation below, the SAB recommends revision of several definitions in the glossary to make them consistent with current science and reduce confusion to the reader.

Use of the term "Bioaccumulation" versus "Accumulation" to Describe Metals Concentrations

It is the opinion of the SAB that there should not be a distinction in the Framework between the term "bioaccumulation" to describe metal concentration in aquatic and terrestrial organisms and the term "accumulation" of metals for humans. This is not an accepted distinction in the scientific community. In humans as in other terrestrial animals, the steady-state body burden of many metals is under homeostatic control that balances intake and excretion. However, for certain metal compounds bioaccumulation can occur, which can be defined as either a persistent increase in individual steady-state levels that is correlated with higher prior exposure, and/or a progressive increase in body burden as a function of exposure time or age, that is above normal steady-state levels and which may involve selective bioaccumulation of the metal in certain tissues.

The SAB believes it important to recognize that some metals do bioaccumulate in the tissues of humans and that this bioaccumulation is related to their toxicity. The rate at which this process occurs depends upon the balance between the accumulation and elimination of the metal in the tissues of concern and, thus, is dependent upon the concentration of the exposure dose and the frequency of exposure. Pharmacokinetic models can be used to estimate the extent to which metals bioaccumulate in tissues. The SAB recommends that the definition of the term "bioaccumulation" in the glossary of this document be modified to read as follows:

> Bioaccumulation: The net accumulation of a metal in a tissue of interest or the whole organism that results from exposure from all environmental sources, including air, water, solid phases (i.e. soil, sediment) and diet, *and that represents a net balance of uptake versus elimination of the metal.*

Metal-specific Reference Values (RfD/RfC) and/or Cancer Potency Factors

The role of the human risk assessor is to appropriately integrate the reference values and potency factors with the exposure assessment. Thus the risk assessor needs an understanding of the toxicological endpoints and mechanisms of action that underlie the derivation of these values to ensure that, for example, the appropriate population and life stages are addressed, appropriate dietary aspects are taken into consideration, and the appropriate exposure pathways are considered. For metals, frequency and duration of exposure, as well as exposure concentrations, are important parameters to be considered for accurate dose assessments. The discussion in the Framework should focus on advising human health risk assessors on how to take these considerations into account in constructing the risk assessment. The SAB recommends that, in introducing the Human Health Effects section, EPA should set the context by explaining that human health risk assessors start their analysis with a metal-specific reference value (RfD/RfC) and/or cancer potency factor that has been developed through a process separate from the risk assessment.

Background Versus Ambient Concentration

The concept of background levels of metals as described in the Framework is not clearly defined. The SAB therefore recommends using the term "ambient" or "ambient levels" rather

than background. The term background is often incorrectly assumed to connote "natural" and therefore "safe" or of no significant human or ecological health concern. However, ambient levels can vary, or can be inherently high enough to represent a potential health concern in and of themselves. They can also represent a total level from a combination of natural and anthropogenic sources, some of which may be historical or unknown. For metals in particular, the concept of background levels as described in the Framework document is complicated by several factors, which include the sometimes highly variable natural levels of metals in soils, sediments, air and water, various historical anthropogenic sources or activities, and air deposition from distant anthropogenic sources. This is also discussed in detail in the response to charge question 3.8 below. The SAB acknowledges, however, that the term "background" exposure has been used in human health dose response assessment. This term, referring to both the natural and anthropogenic sources of a chemical under assessment, has been used in various publications on dose-response modeling over the past 25 years or more.

Chemical Speciation

Among risk assessors and scientists working on metals, the concept of "chemical species" and "chemical speciation" is fundamental. In the Framework, there are certain instances where the terms are used incorrectly. This is discussed in the response to charge question 3.3 below. The SAB recommends that, in addition to correcting these instances, the speciation concept be introduced in the environmental chemistry part of Section 2, specifically in the "environmental chemistry" principles section, and in the environmental chemistry part of Section 4. Appendix B of this SAB report contains text that is adapted from recent IUPAC recommendations (Templeton et al., 2000). The SAB believes that this material would serve as a suitable starting point for discussions in Section 4 of the Framework.

The SAB also recommends that greater care be taken in distinguishing general descriptions of solid-water "partitioning" processes and the very specific term "partition coefficient." In this context, "partitioning" refers to a general set of processes that controls the distribution of metal among dissolved and solid phases, whereas "partition coefficient" is one specific descriptor of the empirical distribution which is based on the ratio of solid phase to dissolved metal.

Balance of Coverage – Metal Speciation

The SAB commends the EPA for emphasizing approaches that employ a relatively sophisticated understanding of metal speciation in the context of metals risk assessment. While there is an adequate discussion in the Framework of the use of models to estimate metal speciation in water, soil, and sediments, there is insufficient discussion of analytical tools to measure the speciation of a metal. A fuller description of the tools that are currently available to quantify metal speciation in environmental samples, including the strengths and weaknesses of each technique, would be of great benefit to a risk assessor in determining the form and potential effects of metal contamination at a given site, and which tools are most appropriate for a given assessment.

Metals Mixtures

The SAB notes that in virtually all settings, individual metals exist as components of mixtures. Even in their natural settings, metals of concern to a risk assessor are typically mingled with other metals. When the question of risk is posed from the standpoint of pollution episodes, the principle still holds; that is, metals are usually presented to ecological receptors and to humans as a mixture with other metals and/or organics. In all instances and settings, then, the assessor must be aware of the additional materials present in that particular environment when a metal is studied as a potentially hazardous pollutant. These "mixed exposures" can have dramatic effects on the toxic potential of the metal.

Mimicry

The SAB notes that structural similarities of metals, such as similar ionic radii, may result in competition for essential receptors, thus, disrupting normal functions. Examples may include chromate substituting for sulfate or phosphate, Pb replacing Ca or Zn, and Cd substituting for Zn or Ca on important regulatory proteins or enzymes. The degree to which these ionic substitutions occur in target cell populations is dependent upon a number of factors including cellular uptake/excretion of toxic metals, intracellular complexations with metal-binding proteins such as metallothionein or lead-binding proteins and sequestration in lysosomes or inclusion bodies. In this regard, the limited discussion in the Framework of metal-binding proteins should be expanded to include more recent references on all of these potential intracellular metal sequestration depots since they will determine the extent to which molecular/ionic mimicry actually occurs *in vivo* (see response to charge question 3.10).

Balance of Coverage – Data Collection

The SAB finds that the Framework contains insufficient information on appropriate parameters for data collection. Recommendations and supporting information should be presented on the types of field data that are needed (including metal speciation and concentrations, and related system parameters such as pH, redox conditions, organic carbon concentrations, iron concentrations, acid volatile sulfides, etc.), and on the appropriate time and space scales for data collection. Revised procedures and processes that are needed to evaluate the adequacy and quality of the data being used for the metals risk assessment should be discussed.

Biogeochemistry

The SAB notes that a key difference in the fate and transport of metals as compared to organic compounds is in the relationship of metals to biogeochemical cycles. For organic compounds, the coupling to natural biogeochemical cycles is essentially unidirectional from the risk assessment perspective (i.e., the major biogeochemical cycles affect the fate and transport of organic compounds, but not vice versa). Metals interact with the cycles of more elements (especially sulfur and other metals) than organic compounds. In addition, metals can be limiting nutrients or toxicants to organisms that drive the major biogeochemical cycles (e.g., higher plants, phytoplankton, bacteria). The SAB finds that the role of metal biogeochemical cycling is

not adequately addressed in the conceptual model for the risk assessment framework, and in subsequent sections of the report (see response to charge question 2.2).

Modeling

The SAB notes that the Framework accurately reflects the fact that modeling the environmental fate and transport of metals differs in significant ways from modeling organic compounds. However, descriptions of a number of models are included in the Framework with little or no information presented on requirements for: adapting existing models for metals applications, developing new metals-specific models for risk assessment, establishing data requirements for model calibration, or determining suitable techniques for estimating parameter values (and associated uncertainties). Further guidance will need to be developed.

Overarching Comments on Specific Sections of the Framework

- The "principles" provided in Section 2 of the Framework are not fundamental principles. The term, "principles," should therefore be replaced with a more appropriate term such as "factors" or "key issues." The SAB also finds a lack of uniformity in the quality and/or clarity of writing among the parts of Section 2. It is noted that the report of the SAB's 2002 Metals Assessment Plan (MAP) review (EPA Science Advisory Board, 2002) addressed many of the same issues. It is therefore recommended that the SAB MAP report be revisited prior to revision of Section 2 in order to improve the quality and clarity of the writing.

- Section 3 of the Framework should be reorganized to provide more comparability among the parts of the section. Recommendations should be highlighted by minimizing textual justification and cross-referencing justification to Section 4.

- The recommendations in Section 3 of the Framework should be rewritten to clearly express them as recommendations (rather than statements).

- The number of recommendations in Section 3 of the Framework should be reduced by omitting statements and condensing similar or redundant recommendations. Recommendations should also be organized by importance or specificity.

- Revised recommendations in Section 3 of the Framework should not be proscriptive, but suggest options or examples.

- Tables such as those provided in A-2 of the Framework should be included in an appendix. Recommendations for improvements to the tables are provided below in the response to charge question 3.4.

- Section 4 of the Framework should be reorganized to mirror the organizational structure used in Section 3.

- As indicated in the response to charge question 1.1 below, Section 5 of the Framework, "Research Needs", should be removed from the document because the research needs are not supported with interpretative text. A separate, follow-up document identifying and prioritizing research needs would be helpful if it were done in a comprehensive manner.

6. RESPONSE TO THE CHARGE QUESTIONS

In the responses to each of the charge questions below, the SAB provides a section devoted to detailed comments followed by key recommendations to EPA. Many of the SAB recommendations take the form of suggested changes to wording to improve clarity. These can be found in Appendix C. In addition, the SAB has identified each recommendation herein to be either "short-term" or "long-term." Recommendations that, in the opinion of the SAB, can be addressed in less than six months are identified as "short-term" recommendations. Recommendations requiring more time to implement are identified as "long-term" recommendations. The determination of whether recommendations are long or short term is based on the subjective judgment of the SAB. The next version of the Framework is not expected to fully address the long-term recommendations but should acknowledge them.

6.1.1 Charge Question 1.1. Please comment on the overall framework scope and whether it is sufficiently encompassing to allow for the consideration of the broad spectrum of physical and chemical properties, exposures, and effects among inorganic metals and metal compound**s**.

6.1.1.1 Comments in Response to Charge Question 1.1

The SAB generally finds that the overall Framework scope is sufficiently broad and provides an appropriate level of flexibility in addressing issues of concern. However, the SAB has identified a number of specific issues that should be addressed. The SAB finds that the following four specific issues deserve attention in answering charge question 1.1.

Balance Between Science and Guidance

As noted above, the Framework document has features of both a state-of-science document and a technical guidance document. The SAB recommends that the Framework be reviewed and revised to remove any confusion in its intended purpose. If the document is to serve as both a framework and practical guide for risk assessors, the recommendations and guidance in the document should be balanced and organized consistently with this dual purpose in mind. EPA should carefully differentiate material that is presented as "the framework for assessment," "examples to illustrate and clarify framework issues," and "specific instructions." It is also important to note that critical evaluations are needed to ensure that the Framework does not prescribe the use of specific methods or tools for risk assessment that may become obsolete over time.

Treating Human and Ecological Health Risk Assessment in One Document

The SAB agrees that both human and ecosystem health risk assessment need to be in one framework document since the uniqueness of metals compared to organic compounds is germane

to both. However, the document needs to achieve better balance in quality and depth of coverage in the sections on human and ecosystem health. Better integration of the human health and ecological health sections with the environmental chemistry section is also needed.

Expanding and Clarifying the Definition of Metals

The SAB feels that the use of the term "metals and metal compounds" is confusing and does not accurately capture the types of metals EPA intends to cover in the document. The SAB recommends that the introduction section of the Framework provide a definition and nomenclature that is inclusive of metals that do not behave like organic compounds but also delineates the groups and classes of metals covered by this document, including metalloids.

Removing Section on Metal Research Needs

It is the opinion of the SAB that the identification of research needs should not be within the scope of the current Framework. There has not been a thorough review of all research areas, and it is not appropriate in the given context to highlight and identify specific research needs for the future. Therefore, the SAB recommends that the research needs section (Section 5) of the Framework be removed.

6.1.1.2 Key Recommendations in Response to Charge Question 1.1

Short-term

1. The purpose of the Framework should be more clearly defined, and the document should be reviewed and revised to remove any confusion in its intended purpose.

2. The Framework should be reviewed to ensure that it does not prescribe specific methods or tools for risk assessment that may become obsolete over time.

3. The introduction section of the Framework should provide a definition and nomenclature that is inclusive of metals that do not behave like organic compounds, but also delineates the groups and classes of metals covered by the document, including metalloids.

4. The research needs section (Section 5) should be removed from the Framework because the document does not contain a thorough review of all research areas.

Long-term

5. The Framework should be revised to achieve better balance in quality and depth of coverage in the sections on human and ecological health. Better integration of the human health and ecological health sections within the environmental chemistry section is also needed.

6.1.2 Charge Question 1.2. The context of the regulatory application (e.g., site specific contaminated site clean-up, national regulation, or programmatic decision) is a major factor in determining the type of analysis that is appropriate for a

particular assessment. The framework identifies three general categories of assessments, including site-specific assessments, national scale assessments, and national ranking and categorization. With the understanding that screening and detailed assessments occur within the assessment categories, please comment on the utility of these categories in setting the context for discussion of metals assessment.

6.1.2.1 Comments in Response to Charge Question 1.2

In general, the SAB finds that the risk assessment categories listed in the Framework are an appropriate context to cast the relevant issues of metals in comparison to organic compounds. The Framework document needs to consider the important properties of metals in these regulatory contexts.

The SAB, however, recommends that the scope of the categories be more clearly defined at the beginning of the document. For example, the SAB believes that the three categories delineated in the document may actually represent five different aspects of assessment (national screening level assessment, national ranking assessment, national complex assessment, site scale screening assessment and site scale complex assessment). Examples of these kinds of assessments are provided below. Definition of these five assessment categories is necessary because in each category the assessment differs in scope and complexity. Under national ranking and categorization, single metal properties or regional site features can be used. Similarly, at the national level assessment, a single parameter can be utilized or the assessment can incorporate site-specific information. At the site-specific assessment level, however, the approach is more focused. Examples of the types of risk assessment that span the range of complexities referred to above include national level that can be: 1) screening (e.g., comparing ambient water concentrations to water quality criteria), 2) ranking (e.g., a contaminant candidate list for the Safe Water Drinking Act); or 3) complex (e.g., criteria documents). They can also include more site-specific screening such as that required prior to completing an environmental impact statement; and site-specific complex assessments such as those required for Superfund.

The SAB feels that the sections in the Framework following the introduction largely concern site-specific assessment issues. The SAB therefore recommends that the document be edited to represent more balance among the different types of assessment. In addition, the document should include focused discussions and mapping to relevant issues at each level of assessment.

6.1.2.2 Key Recommendations in Response to Charge Question 1.2

Short-term

1. The scope of the general categories of assessments should be more clearly defined at the beginning of the document. Examples of the types of risk assessments that span the range of complexities should be provided.

2. The SAB finds that the sections in the Framework following the introduction largely concern site specific assessment issues, and recommends that the document be edited to represent more balance among the different types of assessment.

6.2.1 Charge Question 2.1. Please comment on whether the discussion of inorganic metals assessment principles is clearly articulated, objective, as defined above, and has utility.

6.2.1.1 Comments in Response to Charge Question 2.1

Section 2 of the Framework is entitled Problem Formulation and Principles. This suggests that Section 2 will provide a concise overview of the Framework. The SAB finds that some changes are needed to make this view of the Framework consistent with recommendations in Section 3 and the detail in both Section 4 and EPA's *Papers Addressing Scientific Issues in the Risk Assessment of Metals* (Issue Papers) (EPA, 2004). The SAB also finds a lack of uniformity in the quality and/or clarity of writing among the subsections in Section 2 of the Framework. In addition, the SAB finds that Section 2 of the Framework has an imbalance of coverage among the principles considered. The SAB provides recommendations to address these concerns and improve the utility, objectivity, and clarity of the document.

Articulation of the Inorganic Metals Assessment Principles

A primary issue that arises concerning the utility of the material in Section 2 of the Framework is applicability of the material at local, regional, and national scale risk assessments. It is the judgment of the SAB that most of the detailed material in Section 2, and indeed throughout the Framework, is relevant to site-specific risk assessment. However, the general descriptions of the "principles" are relevant to larger-scale risk assessments as well as site-specific assessments.

The topics listed in Section 2 of the Framework are not principles but rather factors to be considered. For example, bioaccumulation is a process; the relevant principle is activity. The SAB recommends that the terminology in the Framework be changed. It is recommended that EPA drop use of the word "principles" and instead use "factors to be considered" or "factors." The SAB supports the inclusion of the "key questions" listed under several, but not all, of the factors in the Framework. It is recommended that "key questions" be listed in the front of the subsections for all factors included. This will result in parallel construction and help justify the selection of metal-unique topics to focus on in Section 3. The key questions should identify why factors are important and uniquely need to be considered for metal risk assessments.

The SAB finds a lack of uniformity in the quality and/or clarity of writing among the subsections in Section 2 of the Framework. It is noted that the report of the SAB's 2002 Metals Assessment Plan (MAP) review (EPA Science Advisory Board, 2002) addressed many of the same issues. It is therefore recommended that SAB MAP report be revisited prior to revision of Section 2 in order to improve the quality and clarity of the writing in some subsections. Some of the material in the SAB MAP report may be used in Section 2.

The SAB also finds that Section 2 of the Framework has an imbalance of coverage among the factors considered. For example, the subsections on environmental chemistry and toxicity testing are very brief and other important processes such as dietary and or food web exposure and atmospheric transport to receptors should be discussed under route of exposure. It is recommended that the extent of the discussion in the subsections be reviewed and made more

uniform. Suggestions for specific revisions in this regard are provided below (see especially the recommendations for subsections 2.1.4, 2.1.5, and 2.1.6).

In the context of risk assessment, the factors included in the Framework comprise a fairly complete list, but some important factors have been omitted and should be added to the text. These are the nature and type of source, and the route of exposure. These factors should be added to the list in the Framework and text should be developed to a level of detail that is consistent with the other factors presented. While the two factors noted above are relevant for all contaminants, there are unique aspects of metals sources and routes of exposure that a risk assessor will have to address. Two important processes that should be discussed under route of exposure are trophic (dietary and/or food web) transfer, and atmospheric transport to receptors. In the explanation of trophic transfer, it should be noted that the concentration in the water is not predictive of the concentrations at the highest trophic levels. With regard to atmospheric transport, it should be noted that most metals occur almost exclusively as particles in the atmosphere, and this affects how exposure occurs and the types of effects exerted on receptors.

Objectivity and Utility of Inorganic Metals Assessment Principles

Section 2 of EPA's Framework document provides an overview of the risk assessment framework for metals, including the conceptual model representing the various components of the process and their interlinkages. The SAB finds Section 2 to be of high utility for understanding the context of the recommendations in Section 3 and the importance of the detailed process component descriptions in Section 4. However, the SAB provides the following recommendations to improve the utility, objectivity, and clarity of the document.

- The introductory paragraphs of Section 2 on page 2-1 of the Framework emphasize the need for risk assessments at scales ranging from site specific to national. It would be useful to note the risk assessment factors that are unique to metals. It would be helpful to clearly discuss how the complex properties and reactivity of metals present unique challenges in risk assessment.

- The terms used to describe the various factors introduced in Section 2 also need to be carefully defined. For example, the term "essentiality" is vaguely defined in comparison to the level of detail in text boxes defining "background" and "bioavailability." A more precise definition of essentiality that should be included in the document is, "a metal that participates in and is required for some basic biological process with positive consequences for the organism." Similarly, "bioaccumulation and bioconcentration" could be defined in a text box that incorporates the definitions of "bioconcentrate," "bioaccumulate," and "biomagnify" that are presently in the text. A definition of trophic transfer should also be included in this text box. The SAB also notes that the definition of bioavailability given on page 2-6 of the Framework and in the glossary suggests the units of a rate constant in an uptake equation. This does not fit the intended definition of the term.

- The discussion of "background" in subsection 2.1.1 of the Framework includes references to both naturally occurring and anthropogenically-introduced metals. To

some reviewers, the subsection seemed to imply that risk assessments should focus on metals present above natural system concentrations. The SAB therefore recommends that in this subsection EPA place greater emphasis on the potential for naturally occurring metals to pose as much risk as anthropogenic metals. The SAB notes that arsenic, for example, is naturally occurring but still needs to be regulated. It should be more clearly emphasized in the Framework that background concentrations are not necessarily acceptable concentrations. The SAB also notes that consideration of background is substantially different for risk assessments conducted at local, regional, and national scales.

- The SAB notes that involvement of metals in biogeochemical cycles should be emphasized in the Framework in the discussion under the factor "environmental chemistry." At the ecosystem scale, metal biogeochemical cycling considerations are different for metals than for organic compounds. Since metals do not biodegrade, they are recycled in the environment. Metal cycles are often coupled with nutrient cycles. This has important implications for risk assessment since metal contaminants may not pose a risk in the current environmental scenario under consideration, but they may pose a future risk if their chemistry (e.g., oxidation-reduction conditions) changes. In this context, there may not be any single value of "bioavailable fraction" (mentioned on page 2-2, lines 3-4 of the Framework) of a metal that applies to its fate once discharged to the environment. In the environmental chemistry section, metal fate, transport, and bioavailability should be discussed in the context of biogeochemical cycles.

- The environmental chemistry section of the Framework currently focuses on speciation. The SAB believes that additional issues should be included in this section of the document. Other issues that involve unique considerations for metals include processes affecting metals in sediments, and reactions that incorporate metals in organic compounds such as methylation.

- The "bioavailability" subsection of the Framework (2.1.4) is much longer and more detailed than the other sections. To improve the utility of this part of the Framework, the SAB recommends the following revisions. The conceptual bioaccessibility/bioavailability model shown in Figure 2-2 should be moved to Section 4, as should the "bioaccessibility", and "bioavailability" sections. The first italicized sentence in section 2.1.5 ("Bioaccumulation and Bioconcentration") defines the bioaccumulation issue, but the rest of the section appears to be a scattered set of observations that do not help define what is unique to metals about bioaccumulation, what is of concern with how the issue is used (the specific construct), or how it might be used in risk assessments. The discussion should be revised to address these questions.

- Subsection 2.1.6 ("Acclimation, Adaptation, and Tolerance") is an important component that should be linked to the discussion of essentiality in subsection 2.1.2. Also, subsection 2.1.6 should include the potential costs (e.g., genetic erosion) of the acclimation, adaptation, and tolerance phenomena when or where they occur (some discussion should be brought forward from Section 4), as well as their influence on toxicity testing.

- The Framework addresses those assessment issues associated with inorganic compounds but also discusses natural transformation pathways that form organometallic compounds. The mixtures discussion in the Framework document focuses on metal mixtures. The SAB notes however, that the document should also contain a discussion of interactions between metals and organic chemicals as it applies to the problem of mixtures. Mixtures of metals and certain organic compounds can behave additively, synergistically and/or antagonistically with respect to cancer risk, depending on the mixture and the context. There is ample evidence of this from laboratory experiments with simple mixtures (e.g., arsenic and PAHs) showing a variety of complex effects not well predicted by knowledge of either agent alone. In addition, it would be useful to include a discussion indicating that metals can react with organics to form organometallic compounds, thus transforming a metal to a state in which its fate and risk will be governed by processes more relevant to organic compounds (e.g., biodegradation, partitioning to dissolved organic carbon [DOC]).

6.2.1.2 Key Recommendations in Response to Charge Question 2.1

Short-term

1. EPA should drop the use of the word "principles" in the Framework and instead use "factors to be considered" or "factors."

2. EPA should list "key questions" in the front of appropriate Framework subsections for all factors included.

3. EPA should revisit the SAB Metals Action Plan report (EPA Science Advisory Board, 2002) prior to revision of Section 2 of the Framework in order to improve the quality and clarity of the writing in some subsections.

4. EPA should review the extent of the discussion in all parts of Section 2 of the Framework and make it more uniform. Suggestions for specific revisions in this regard are provided above (see the recommendations for subsections 2.1.4, 2.1.5, and 2.1.6).

5. Some important factors that have been omitted from the Framework should be discussed in the text. These factors are: the nature and type of source, and route of exposure.

6. Risk assessment factors unique to metals should be identified in the text of the Framework. The document should discuss how the complex properties and reactivity of metals present unique challenges in risk assessment.

7. EPA should carefully define the terms used to describe various factors introduced in Section 2 of the Framework.

8. EPA should place greater emphasis in the Framework on the potential for naturally occurring metals to pose as much risk as anthropogenic metals.

9. The Framework discussion of environmental chemistry should emphasize the involvement of metals in biogeochemical cycles.

10. The environmental chemistry section of the Framework should include a discussion of processes affecting metals in sediments, and reactions that incorporate metals in organic compounds such as methylation.

11. The "bioavailability" section of the Framework should be revised to define what is unique to metals about bioaccumulation and how this information might be used in risk assessments. EPA should move the conceptual bioaccessibility/bioavailability model and related discussion to Section 4 of the Framework.

12. The important Framework discussion of acclimation, adaptation, and tolerance should be linked to the discussion of essentiality.

Long-term

14. EPA should revise the Framework to include a discussion of assessing the risks of metal/metal contaminant mixtures as well as metal/organic contaminant mixtures.

6.2.2 Charge Question 2.2. Please comment on how well the conceptual model presents key metal processes and whether or not it is complete.

6.2.2.1 Comments in Response to Charge Question 2.2

The SAB finds that the conceptual model in the Framework is sufficiently comprehensive. However, the conceptual model should be more clearly linked to text in various parts of the Framework. The SAB recommends revisions to improve presentation of the conceptual model and to emphasize key concepts in the model.

Completeness of Conceptual Model

The conceptual model as depicted in Figure 2-3 of the Framework is sufficiently comprehensive. It is closely related to a conventional multimedia exposure model. A key difference between metals and most organic compounds with respect to fate and transport is the biogeochemical cycling of metals. The role of biogeochemical cycling in the conceptual model for metals does not appear to be adequately represented in Figure 2-3, though it may be considered under the "Environmental Chemistry" (M1) part of the diagram. At a minimum, the text related to Figure 2-3 should mention the role of biogeochemical cycling. As currently presented, the conceptual model lacks the feedbacks involved in biogeochemical cycling.

Linkage of Conceptual Model to Text in the Framework

The SAB notes that Figure 2-3 of the Framework is a compact summary of the conceptual model upon which the risk assessment framework is based. The text in the various parts of Section 2 should therefore be related to Figure 2-3. This can be accomplished with some modest

revision of the existing text. More detail will be needed in some parts in order to explain the relevance of some of the components of Figure 2-3 not currently addressed in the text (e.g., transport models). In revising the parts of Section 2 to explain linkage with the relevant components of Figure 2-3, links to related parts of Sections 3 and 4 should be included where appropriate.

The SAB finds that Figure 2-2 of the Framework is also an important organizing graphic, but it focuses on detailed processes that are not discussed in detail in Section 2 of the document. As Section 2 is an overview of basic factors to be considered in metals risk assessment, Figure 2-2 is too detailed to be included in this section. Figure 2-3 provides the high level of aggregation appropriate for Section 2. Figure 2-2 is well structured and informative, but should be moved to Section 4 where it can be introduced and explained in detail, and linked to the topics discussed in that part of the Framework document.

Key Concepts to be Emphasized in the Conceptual Model

The conceptual model in the Framework is closely related to conventional organic multimedia models, both in the component models chosen and in the linear sequence in which they are applied. Much of the Framework is devoted to distinguishing concepts used in metals risk assessment from organic risk assessment. The following key concepts that are not indicated in the conceptual model diagram should be emphasized either by modifying the diagram or by adding accompanying text where Figure 2-3 is introduced:

- Precipitation/dissolution of mineral phases that contain a metal can lead to a decoupling of the usual linear relationship between the total mass of a metal in an environmental compartment and the free ion or other dissolved metal concentrations.

- Cyclical metal transformation processes, such as oxidation/reduction and methylation/demethylation, are not readily handled by organic fate and transport models since metal reactions do not result in a permanent transformation to another compound.

- Natural loadings of metals differ from anthropogenic loadings in that they may come from inside the system of interest at rates controlled by natural processes.

- The fate and transport of both organic compounds and metals are coupled to the major biogeochemical cycles, such as carbon and nutrients. In general, metals interact with the cycles of more elements (especially sulfur and other metals) than organic compounds. For organic compounds, the coupling to natural biogeochemical cycles is essentially unidirectional (i.e., the major biogeochemical cycles affect the fate and transport of organics, but not vice versa). For metals, exceptions to this rule are more common since metals can be limiting nutrients or toxicants to organisms that drive the major biogeochemical cycles such as higher plants, phytoplankton, or bacteria. This aspect of metal biogeochemistry cannot be simply accounted for in a linear framework. In the absence of a comprehensive model, a means of allowing metals model outputs to feed back into values selected for model input parameters that govern the major cycles may need to be devised.

- The "metalloregions" approach (briefly discussed on page 2-12 of the Framework) of defining "metal-related ecoregions" for regional or national-scale assessments is an evolving approach that may have merit. Because no details on the approach are presented in the Framework, however, it is difficult for the reader to evaluate the strength of its potential value. The SAB recommends that an expanded description of the approach be provided, and that it be presented as just one example of how regional-scale risk assessment might be approached. The challenges that result from uncertainty and variability inherent in the approach should be addressed.

6.2.2.2 Key Recommendations in Response to Charge Question 2.2

Short-term

1. Text related to the model depiction in Figure 2-3 of the Framework should mention the role of biogeochemical cycling.

2. Text in various parts of Section 2 of the Framework should be related to Figure 2-3. In revising parts of Section 2 to explain linkage with components of Figure 2-3, links to related parts of Sections 3 and 4 of the Framework should also be included.

3. Figure 2-2 of the Framework should be moved to Section 4 where it can be introduced, explained in detail and linked to the topics discussed in that part of the Framework.

4. The following key concepts should be emphasized in the conceptual model by modifying Figure 2-3 or adding accompanying text: precipitation/dissolution of mineral phases containing metals, cyclical metal transformation processes, and natural loadings of metals.

Long-term

7. Because metals can be limiting nutrients or toxicants to organisms that drive major biogeochemical cycles, the conceptual model should incorporate feedback into model input parameters that govern biogeochemical cycles.

8. An expanded description of the "metalloregions" approach of defining "metal-related ecoregions" should be incorporated into the Framework.

6.3.1 Charge Question 3.1. Please comment on how well the recommendations under Section 3 are supported by the detailed information in Section 4. Are there recommendations that should be included? Are there any inorganic metals or metal compounds for which any of the recommendations would not apply?

6.3.1.1 Comments in Response to Charge Question 3.1

The SAB has reviewed the recommendations in Section 3 of the Framework document and provides the following comments. To be most helpful, the recommendations should be tiered, with the most critical general overarching recommendations (those with the greatest impact)

presented first, followed by other specific recommendations that would be of value to the assessor. This would help focus the different sections of the Framework to ensure that the most important issues are addressed. Tiered recommendations would also provide a platform for subsequent documents so the assessor can prioritize how a risk assessment site is addressed. Tiering options might involve restructuring all of Section 3 or developing tiered recommendations within individual subsections. The SAB notes that recommendations pertaining to various topics in the Framework are distributed throughout Section 3 of the document. For example, recommendations pertaining to environmental chemistry are included in Sections 3.2.1 and 3.3.1 that present recommendations on environmental fate and transport.

General Comments on the Recommendations in the Framework

The SAB provides the following general comments on the recommendations in the Framework.

- To ensure that the document is not prescriptive, as stated in the document purpose in Section 1, the SAB recommends that prescriptive recommendations throughout the document be generalized. For example, instead of recommending a particular model or approach (such as recommendation 3 on page 3-24), the models should be described as alternatives among several approaches.

- Section 3 of the Framework should be reorganized to make it internally consistent with other parts of Section 3. For example, the headings for aquatic risk assessment should be more similar to those for terrestrial risk assessment. There is a lack of parallelism between the aquatic and terrestrial recommendations and balance needs to be achieved. The terrestrial recommendations, in general, include a broader range of approaches and include specific guidance to the risk assessor regarding the current state-of-the science (i.e., tools for today) as well as the direction of future tools and approaches. A similar level of guidance and recommendations needs to be reflected in the aquatic discussion.

- Recommendations should be highlighted by minimizing textual justification, and cross-referencing the justification directly to those parts of Section 4 that support or discuss the recommendations. Additionally, any references to the scientific literature that are contained in the recommendations should be removed. References should be provided in the sections of the Framework that support the recommendations.

- As opposed to the broad environmental chemistry recommendations given in Section 3.2.1 of the Framework, the recommendations provided at the end of Section 3.3.1 (pages 3-23 and 3-24) are very specific. The SAB notes that it is unclear whether this level of specificity is appropriate for a "Framework" document. A greater degree of consistency is needed with respect to the specificity of the recommendations as a whole.

- In general, the environmental chemistry recommendations in Section 3 are supported by the discussion in Section 4. However, it is difficult to determine which parts of Section 4 correspond to particular recommendations in Section 3. In order to better assess the support for the recommendations in Section 3, it would be helpful to provide a "section

identifier" indicating the source of the supporting information. Similarly, this might serve as a better way to organize Section 4.

- The focus of many of the environmental chemistry recommendations is on modeling. However, little information is provided on activities related to model validation or other data collection efforts that may be important for a given location. For example, the complex environmental conditions at a specific site may not be amenable to application of available models and may require substantial site-specific data.

- While it may be logical to separate the discussion of soil and sediment for the purposes of assessing exposure or toxicity, the SAB finds that from an environmental chemistry perspective it would be preferable to combine the discussion of the two media in one section. In this format, geochemical origins and resulting similarities among soils, aquatic sediments, and subsurface sediments can first be highlighted. Risk assessment approaches that have evolved to depend upon different factors such as controlling solid phases, solution composition, and redox conditions, can then be discussed.

- The SAB recommends that EPA reduce the number of specific recommendations in the Framework by omitting statements that are not recommendations and condensing similar or redundant recommendations.

Comments on Recommendations in Specific Sections of the Framework

The SAB has numerous comments addressing the question of whether the recommendations set forth in Section 3 of the Framework are directly supported by the more detailed discussion in Section 4 and are justified or germane to an understanding of the risks of metals. The SAB believes that some recommendations should be deleted and others amended. The SAB also believes that additional recommendations should be considered for inclusion in the Framework document. Detailed comments, organized by section number of the Framework, are provided in Appendix A of this report.

6.3.1.2 Key Recommendations in Response to Charge Question 3.1

Short-term:

1. EPA should provide tiered recommendations in the Framework. To be most helpful the most critical recommendations should be presented first, followed by specific recommendations that would be of value to the risk assessor.

2. Prescriptive recommendations throughout the Framework should be generalized. Alternative choices should be described instead of recommending a specific approach or method.

3. Section 3 of the Framework should be reorganized to make the parts of the Section internally consistent in scope and balance.

4. The recommendations in the Framework should be highlighted by minimizing the amount of text in Section 3, cross-referencing the justification directly to appropriate parts of Section 4 of

the document.

5. EPA should revise the Framework to provide a greater degree of consistency with respect to the specificity of the recommendations.

6. With regard to recommendations concerning modeling, EPA should provide more information on model validation or data collection efforts that may be important for a given location.

7. The discussion of soil and sediment should be combined into one section.

8. EPA should reduce the number of specific recommendations in the Framework by omitting statements that are not recommendations and condensing similar or redundant recommendations.

9. EPA should address detailed comments and suggestions provided in Appendix A of this report. The detailed comments in Appendix A focus on the question of whether recommendations in various sections of the Framework are directly supported by the discussion in Section 4 of the document.

6.3.2 Charge Question 3.2. Please comment on the objectivity and utility of the data, tools, and methods discussed in Section 4. Identify any scientific or technical inaccuracies, or any emerging areas or innovative applications of current knowledge that may have been overlooked or warrant a better discussion of uncertainty, including areas needing further research.

6.3.2.1 Comments in Response to Charge Question 3.2

The SAB finds that the human exposure and health effects discussion in Section 4 of the Framework is not complete and contains errors. The SAB finds that this part of the Framework will require a major rewrite that may not be achievable in the short-term. However, such a rewrite will be essential if the treatment of human exposure and health effects is to be of equal value to other parts of the Framework. The environmental chemistry discussion in Section 4 of the Framework is comprehensive, but in many instances critical evaluations of the tools and methods are not provided and the justification for many recommendations is not clear. The ecological exposure and effects discussion in Section 4 of the Framework provides a great deal of supporting information for the recommendations articulated in Section 3 of the document. However, the treatment of various topics addressed in this part of the Framework is uneven. The SAB provides recommendations for improvements in the document.

Human Exposure and Health Effects

Much of the human health information in Section 4 was derived from the issue paper on human health effects of metals (EPA, 2004), which was not comprehensive and needs to be expanded to improve this key resource for the Framework document. The following are examples of key items that need to be addressed.

- The SAB notes the importance of considering nanoparticles and their associated metal content in assessing human exposure to metals. Dermal exposure is also of considerable

importance with regard to nanoparticles.

- The SAB notes that PM_{10} and $PM_{2.5}$ need greater attention as mixtures with regard to human exposure and health effects.

- The SAB notes that the discussion of Hg speciation was not given sufficient attention especially with regard to the source of exposure. Additionally, Hg speciation *in vivo* is very complex and measurements of blood Hg levels generally do not distinguish between, for example, dental exposure to metallic Hg vapor and Methyl Hg from eating fish.

- There is reference in Section 4 of the Framework to the principle of metal accumulation in organisms that can be eaten by humans. The SAB notes that and this general principle applies to many metals but not all metals. In vivo speciation of some metals may occur. For example, plants, fish, and game that take up hexavalent Cr can convert it to the less toxic trivalent form. Thus, humans can safely consume most plants and animals exposed to hexavalent Cr.

- The SAB notes the omission of any discussion in Section 4 of toxic effects of metals at low doses. This is a crucial issue because a number of metals exhibit a biphasic dose response curve with distinct adverse effects at low doses and a different type of toxic response at higher concentrations. The SAB recommends the inclusion of a section in the Framework that describes low dose toxic responses to metals and their compounds. For example, it is now apparent that Pb exhibits a biphasic dose-response curve with a greater slope of toxicity versus blood Pb concentrations at low exposure levels.

- The SAB suggests that Section 4 should include an analysis of: 1) the extent to which the use of Benchmark Dose Modeling decreases uncertainty and improves the derivation of RfDs for metals compared to the use of no observed adverse effects levels (NOAELs), and 2) the importance of updating current RfDs using the Benchmark dose modeling approach.

- The SAB notes the importance of including more summary tables in the Framework to enhance the understanding of the complex information presented in section 4.

- The SAB notes an insufficient discussion of the interactions between metals and organic chemicals as it applies to the problem of mixtures. There needs to be more discussion in the Framework of how metals interact with organics and how this interaction can lead to potentiation or antagonism. The SAB also notes the importance of applying proper objective criteria to assessing these interactions, including correct statistical tests.

Environmental Chemistry

The SAB finds that, with respect to environmental chemistry, the coverage of available tools for risk assessment and methods for metals analyses is fairly comprehensive, with an emphasis on tools and methods unique to metals. Detailed descriptions of tools and methods are not given in the Framework, but adequate references are cited. In many instances however, critical

evaluations of the tools and methods are not provided and the justification for many recommendations is not clear. Two examples are given below:

- In recommending analytical techniques to characterize metal speciation (page 3-23, lines 6-13), no evaluations were presented in Section 4 to help distinguish between methods commonly available through contract laboratories and those that presently are only available through research universities and laboratories.

- In recommending computer modeling to predict metal speciation in soil solutions (page 3-23, lines 15-18), the computer programs Windermere Humus Aqueous Model (WHAM) and Non-Ideal Competitive Absorption Model (NICA) are cited without any discussion in Section 4 of the strengths, weaknesses, and limitations in the modeling approaches.

The SAB therefore recommends that more emphasis be placed on developing comparative assessments of available tools and methods, and on providing additional information to aid risk assessors in deciding when particular tools and methods are and are not appropriate.

The SAB also recommends that the balance of coverage in Section 4 be reviewed. The following issues are cited:

- Modeling tools, and to a lesser extent, analytical methods are included in the Framework. Limited information however is provided on what should be considered in data collection efforts (e.g., such as the type of data to be collected, appropriate temporal and spatial time scales to be considered, and data quality requirements that are unique to metals evaluations).

- EPA should provide a more balanced discussion of approaches for measuring solution speciation versus techniques for assessing solid phase speciation. In Section 4, no mention is made of current methods to assess free metal ion concentrations in the solution phase for some metals directly (e.g., through specific ion electrodes, voltametry, or standard EPA methods) or for measuring solution speciation for some metalloids.

- Although it could be argued that several of the modeling tools presented apply equally well to marine and freshwater systems, specific issues for the marine environment (e.g., background concentrations and ion strength corrections) are barely addressed in comparison to the specific issues for freshwater environments.

The SAB also recommends that Section 4 of the Framework contain additional consideration and discussion of data requirements and model uncertainty. Issues that should be addressed include: criteria for designing a sampling plan, data requirements for model calibration, suitable techniques for estimating parameter values (and associated uncertainties) for simple and complex models, and evaluation of model uncertainty in model simulation results that are specific to metals.

In addition, the SAB recommends that biogeochemical cycles be discussed in Section 4 of the

Framework. This discussion should include the effects of organic carbon (and possibly iron and manganese) on the fate of metals in the environment, and the effects of metals on organic carbon and other ecological cycles through nutritional limitations or through toxic response.

Ecological Exposure and Effects

With respect to ecological exposure and effects, the SAB finds that Section 4 of the Framework offers a great deal of supporting information for the recommendations that are articulated in Section 3. However, the manner of treatment for the various parts of Section 4 relative to ecological metals risk assessment should be more parallel in format across the pathways of exposure. This is particularly evident in the uneven treatment of topics such as aquatic sediment and bulk sediment chemistry in comparison to the treatment of soils. A critical shortcoming of the treatment of ecological metals risk assessment is the lack of a discussion of levels of uncertainty, both in the knowledge base as well as in metals risk assessment implementation. A discussion of uncertainty should be more explicit and more uniformly distributed throughout the presentation of the current state of knowledge. The following specific shortcomings are noted.

The Biotic Ligand Model (BLM) approach is highlighted in Section 4 of the Framework but the reader is never provided with a clear definition of the concept. The concept is treated as though the reader is already familiar with this approach. It is the opinion of the SAB that the BLM concept should be clearly defined. Trophic transfer is discussed extensively in Section 4 of the Framework but not with respect to the BLM.

There is very little attention given in Section 4 of the Framework to the importance of parameter, model, and laboratory validation in the field. There is a great deal of emphasis in this section on models as tools for metals risk assessment as appropriate, but the section lacks a discussion of field validation needs and the consequences of this deficiency in the current state of knowledge. There is little discussion of ecosystem assessment or habitat assessment, the discussion focuses on biotic indicators only.

Section 4 of the Framework contains a good discussion of dietary exposure and trophic transfer but the tools to deal with these processes are not comparably developed. For example, tools such as dynamic modeling (i.e., biodynamic or biokinetic modeling) should be included in the discussion.

Section 4 of the Framework should also include a discussion of acclimation and adaptation. This is discussed in more detail in the response to charge question 3.11. Species sensitivity distributions (SSDs), mentioned in Section 4 but not discussed, should be more fully described in this section. There is limited discussion of vascular plant risk assessment for metals and this topic could be further developed in a manner parallel to other sections of the chapter.

6.3.2.2 Key Recommendations in Response to Charge Question 3.2

Short-term

1. The discussion of mercury speciation in the Framework should be given greater attention, particularly with regard to the source of exposure.

2. EPA should clarify the discussion of the principle of metal accumulation in organisms to indicate that it does not apply to all metals; in vivo speciation changes must be considered.

3. A discussion of toxic effects of metals and metal compounds at low doses should be incorporated into Section 4 of the Framework.

4. An analysis of the extent to which use of Benchmark Dose Modeling decreases uncertainty and improves derivation of RfDs for metals compared to the use of no observed adverse effects levels should be incorporated into the Framework.

5. EPA should include more summary tables in the Framework in order to enhance the understanding of the complex information presented in Section 4.

6. EPA should place more emphasis in Section 4 of the Framework on comparative assessments of a available tools and methods, and on providing additional information to assist risk assessors in deciding when particular tools and methods are, and are not, appropriate.

7. In Section 4 of the Framework EPA should provide a more balanced discussion of approaches for measuring solution speciation versus techniques for assessing solid phase speciation.

8. A discussion of biogeochemical cycles should be incorporated into Section 4 of the Framework.

9. In Section 4 of the Framework EPA should provide a more balanced discussion of exposure pathways relative to ecological risk assessment. The treatment of topics such as aquatic sediment and bulk sediment chemistry is particularly uneven in comparison to the treatment of soils.

10. The Biotic Ligand Model concept should be more clearly defined in Section 4 of the Framework. Trophic transfer is not discussed with respect to the Biotic Ligand Model.

11. Section 4 of the Framework should contain a discussion of tools such as dynamic modeling (i.e., biodynamic or biokinetic modeling) to deal with dietary exposure and trophic transfer.

12. The ecological exposure and effects part of Section 4 of the Framework should contain a discussion of acclimation and adaptation.

Long-term

13. The Framework should address the importance of considering nanoparticles and their associated metal content in assessing human exposure to metals.

14. In the Framework, PM_{10} and $PM_{2.5}$ mixtures should receive greater attention with regard to human exposure and health effects.

15. The Framework should contain more discussion of how metals interact with organic compounds, and how this interaction can lead to potentiation or antagonism.

16. The Framework should contain more information on factors to be considered in data collection for metals evaluations (e.g., type of data, temporal and spatial time scales, and data quality requirements unique to metals).

17. The Framework should contain additional information on modeling issues to be considered in the marine environment (e.g., background concentrations and ion strength corrections).

18. Section 4 of the Framework should contain additional information to address model uncertainty and data requirements.

19. The Framework should contain a more explicit discussion of uncertainty in ecological risk assessment of metals.

20. The Framework should contain a discussion of field validation needs for models.

6.3.3 Charge Question 3.3. Please comment on the state of the science (i.e., data, tools and methods) to address inorganic metals speciation in all environmental compartments for any given inorganic metal from the point of environmental release to the point of toxic activity as discussed in the document. Please comment on whether the framework identifies appropriate research needs to overcome any limitations in the state of the science. Please address these questions separately for each of the three types of assessments presented (i.e., site-specific, national level, and ranking and categorization.)

6.3.3.1 Comments in Response to Charge Question 3.3

The SAB finds that the discussion of speciation in the Framework could be improved by bringing this information together and placing it in one part of the document. As discussed below, the SAB also finds that additional information relevant to the subject of metals speciation should be included in the Framework. In addition, the SAB finds that the research needs section of the Framework appears to be a collection of limitations with no systematic or comprehensive development of the limitations. The SAB therefore recommends that the limitations be discussed in Section 4 of the Framework and that Section 5 of the Framework be removed from the document.

The SAB notes that the major limitation in addressing inorganic metal speciation in risk assessment is the lack of good analytical tools for the direct measurement of metal species/fractions. However, tools to directly measure metal species do exist and are improving with time. The need to develop these tools, and the data to support modeling of speciation, should be discussed in the Framework. The SAB feels that the Framework should not recommend specific analytical tools, but it should discuss the importance of determining speciation in environmental media and human biomonitoring samples. The paucity of data to support modeling of speciation limits the risk assessor's ability to adequately include speciation in metal risk assessment tasks at site and national scales. The SAB notes, however, that metal

speciation determination is more applicable for site-specific investigations than the setting of national standards.

The lack of analytical tools for direct measurement of metal species/fractions affects models related to environmental transport and fate as well as exposure. Section 5 of the Framework lists research needs that would address this limitation but these needs are only listed in a bulleted form. In comparison, the discussion of the Unit World Model, which may address other risk assessment needs, is more extensive. The SAB notes that all research needs should be addressed at a similar level of detail if this section of the document is to have relevance. As it stands now, this section is just a collection of limitations with no systematic or comprehensive development of them. It would be preferable to include these limitations within the discussions of Section 4 and omit Section 5 of the Framework.

The SAB provides the following specific comments in response to charge question 3.3.

- The SAB notes that it would be useful to collect the discussions of metal speciation in one location in the document.

- The Framework should contain a discussion of how to bound uncertainty in site and national efforts employing speciation.

- The SAB notes that a section needs to be added to the Framework on the importance of speciation of metals in human toxicity from the point of view of exposure and the diversity of species that can be formed within the body, (i.e., Cr (VI) and Cr (III), As methylation, elemental Hg and inorganic Hg, Cd metallothionein and other Cd ligands, etc.). It is important to identify the chemically and toxicologically active species of the metal as well.

- The SAB notes the importance of developing techniques to measure, in biological tissues, different species of metals to which humans can become exposed as well as to understand the species formed within the human body (e.g., methylated forms of As, and Cr oxidation states). This should be addressed in the Framework.

- The SAB notes the importance of considering metal speciation for each individual metal since this concept makes sense only when considering each individual metal.

- The SAB notes that numerous tools in the form of models and operationally defined analytical methods to address inorganic metal speciation are listed and discussed in the Framework. There are several well developed models for establishing the theoretical distribution of metals among species for given conditions in solution, although only specific ones are considered in much detail in the Framework. Similar models for understanding speciation in other media, such as soils and sediments, are not as well developed. As noted above, however, analytical tools to measure inorganic metal species are not very advanced. Analytical tools that are discussed in the Framework (e.g. simultaneously extracted metals [SEM], sequential extractions) are, in reality, methods designed to fractionate an environmental matrix. With regard to application of these

tools to the three types of assessments discussed in the Framework, models using the Hard and Soft Acids and Bases (HSAB) concept are probably most suitable for national assessments. The other tools appear to be applicable across the assessment types.

- The SAB notes that all discussions in the Framework that are related to speciation should adhere to the definition in the glossary. The use of consistent terminology when discussing forms of metals in various environmental matrices is recommended. This is discussed more fully in Appendix B of this report where a terminology proposed by an international expert body is provided.

- The SAB finds that the discussion of inorganic metals speciation is well developed in the Framework, and is successful in describing the importance of inorganic metals speciation in determining biological or ecological risk. However, the focus of the discussion is largely on the metal cations of greatest commercial interest, which represent only about one third of the metals of interest identified in the Framework scope (Section 1.2). The speciation section of the Framework should discuss all of the metals of interest, particularly the anionic metals Se, Sb, As, and V for which speciation is critically important in mobility and toxicity. The discussion of inorganic metals speciation should also clearly address metals that do not behave like the metal cations.

- The discussion of speciation in the Framework should include a biogeochemical context which provides a more complete understanding of processes influencing metal exposure and metal transformations. The discussion should point out where methods are available to directly measure metal species of interest and where modeling is the most suitable approach.

- The SAB finds that the Framework is selective in its treatment of speciation and transformations in the water column and in sediment, and would benefit from a more parallel organization of the discussion.

6.3.3.2 Key Recommendations in Response to Charge Question 3.3

Short-term

1. The limitations in the research needs section of the Framework should be included in the discussion in Section 4 of the Framework and Section 5 of the Framework should be removed from the document. This revision is needed because the research needs section of the Framework appears to be a collection of limitations with no systematic or comprehensive development of the limitations.

2. EPA should collect the discussions of metal speciation in one location in the Framework.

3. A section on the importance of speciation of metals in human toxicity should be added to the Framework.

4. EPA should use consistent terminology when discussing forms of metals in various environmental matrices. The discussion in the Framework that is related to speciation should

adhere to the definitions in the glossary.

5. The Framework discussion of inorganic metals speciation should include all metals of interest (not just metal cations of greatest commercial interest), particularly the anionic metals, Se, Sb, As, and V, for which speciation is critically important in mobility and toxicity.

6. The Framework discussion of speciation should include a biogeochemical context that provides a more complete understanding of processes influencing metal exposure and metal transformations.

Long-term

7. The Framework should contain a discussion of analytical tools for the direct measurement of metals species/fractions. The Framework should not recommend specific analytical tools, but it should discuss the importance of determining speciation in environmental media and human biomonitoring samples.

8. The Framework should contain a discussion of how to bound uncertainty in site and national efforts employing speciation.

6.3.4 Charge Question 3.4. In an earlier draft of the framework, EPA had included three Summary Recommendation Tables in Section 3 on human health, aquatic, and terrestrial risk assessment, covering the three general assessment categories (i.e., site-specific, national level, and ranking and categorization). An example of this table is included as Appendix A in the draft provided to the SAB. To minimize confusion for users of the framework, the initial idea behind the recommendations and adjoining table was to have concise recommendations on the science, followed by a separate accounting of how these recommendations could then be applied to the different assessment categories. Reviews have been mixed on the utility of these tables as a sufficient communication tool. Please comment on whether tables of this type are useful for the final version of the framework. Does the panel have alternative suggestions for effectively communicating how the recommendations can be considered for each of the three assessment levels?

6.3.4.1 Comments in Response to Charge Question 3.4

In general, the SAB finds that Summary Recommendation Tables such as the example presented in Table A-1 of the Framework are a good way to summarize important points and capture the structure character of the document. Tables have an advantage as a way of presenting a summary, arranging complicated material to allow it to be viewed from different perspectives, and facilitating organizing and cross referencing of materials. However creation of a summary table for a complex document such as the Framework is not straightforward. Issues that arise include: the difficulty of representing complex concepts in short statements in the table; the temptation to accept the abbreviated representation of the material in the table and ignore the full complexity of the matter; and the fact that as the length and completeness of the table

increases, it expands across multiple pages and loses the advantage of a compact representation of the material.

The SAB recommends that the tables in the Framework be formatted differently and moved forward to a "lead" position near the beginning of Section 3. The tables should be structured to capture the recommendations presented in Section 3 in an organized manner that relates them to their utility for the categories of risk assessment discussed in this document (i.e. national ranking and categorization, national level assessments, and site specific assessments), with recognition that within these three categories there are both screening and definitive risk assessments. In this regard, the tables should include key but limited information on currently available tools as well as future tools and methods not yet readily available for use in operational risk assessment activities. The tables should provide, at a glance, an outline of the framework, key elements of the framework recommendations, and available approaches (now and in the near future) to accomplish these metals risk assessment goals. Use of the term "tools" as presented in the Table A-1 needs to be reassessed, because "fate and transport" and "bioaccumulation" are not specific tools, but are aspects of risk assessment that require application of specific tools (e.g., extraction techniques for estimating bioavailability).

The SAB recommends that the tables not include references to the scientific literature but rather references to the specific parts of Section 4 of the Framework to explain the information and recommendations in the table. Table footnotes could be added to reference the relevant sections of the text and provide justification for each recommendation listed and summarized in the table. In this way, the tables become an operational, rapid index to the document. Such tables, if created for each of three broad subject areas covered in the Framework (i.e., ecological exposure and effects, human exposure and health effects, and environmental chemistry), would help ensure consistency between the three areas. These tables could be placed at the end of each relevant part of Section 3. The SAB notes that an alternative to using summary tables as a way of complementing the text would be to include a series of examples.

Section 4 of the Framework should provide: 1) a thorough discussion of the background science that supports the rationale for the framework structure and recommendations, 2) a practical overview of current practice and the technical and political context of those activities, and 3) a discussion of opportunities for improved approaches in metals risk assessment now and in the future. Section 4 should embody a state of science analysis that leads to sound assessment practices, and thereby highlights some of the logical research needs in the metals risk assessment arena. Section 3 of the Framework should ideally include much less text, focusing on providing the broader intent and context for the table.

Table 1 below illustrates a possible approach to capturing the elements of the Framework into a table, and providing a gateway to the information contained in Section 4 of the document. The SAB notes that there are other approaches. It is suggested that the challenges in developing tables will be identifying brief descriptors of key elements of the Framework recommendations, providing appropriate references to the sections of the document that fully discuss these sometimes complex issues, and ranking otherwise complex and subjective aspects of information related to each recommendation such as uncertainty. The SAB suggests that the overriding benefit of developing tables will be providing a visual summary of the essence of the Framework

that offers information of value to metal risk assessors and directions to relevant information in the document. Table 1 below is a skeletal representation of a possible table structure, with an ecological exposure and effects example filled in for the purpose of illustration.

6.3.4.2 Key Recommendations in Response to Charge Question 3.4

Short-term

1. Summary Recommendation Tables in Section 3 of the Framework should be reformatted and moved to a lead position near the beginning of Section 3.

2. The summary recommendation tables should not include references to the scientific literature, but rather references to the specific parts of Section 4 of the Framework that explain the information and recommendations in the tables.

Table 1.

DRAFT RECOMMENDATIONS TABLE – FRAMEWORK FOR METALS ASSESSMENT										
No.	Recommendation	National Screening	National Ranking	National Complex	Site Scale Screening	Site Scale Complex	Tools Current	Tools Future	Uncertainty	Data Issues
	Chapter HUMAN									
1										
Ref										
2										
Ref										
	Chapter AQUATIC									
3	BLM for use in assessing bioavailability	1	1	1	1	1	1		1	1
Ref	4.3.2		4.4.4.1	4.8.1	x.x.x.x	x.x.x	x.x.x.x.x	x.x.x.x	x.x	x.x.x
4										
Ref										
5										
Ref										
	Chapter TERRESTRIAL									
6										
Ref										
7										
Ref										

Notes on Table 1:

- Each recommendation in the table would occupy a block, but not all cells would be filled in. In most cases Current and Future tools available would not be filled in, particularly when the recommendations deal specifically with a tool. Where specific tasks are recommended, it is possible current and future tools would exist.

- Most cells would be filled by a numeric system where 0 = not good or not applicable, 1 = somewhat available/applicable or other qualifier, and 2 = excellent option or application. No verbiage is included in the BLM example although it is possible that a few words might accompany the numbers in the boxes.

- With each recommendation there is a row that includes references to the parts of Section 4 of the Framework. Only single sections are listed although multiple pointers could be included in any box, and should represent the roadmap to the relevant discussions.

- Uncertainty is an important column even though it is highly subjective. Including this column highlights the need to consider the uncertainty in the approach or tools being used by the risk assessor, and offers a judgment of how much uncertainty is associated with that approach or factor or tool in risk assessment could be due to natural factors, characteristics of the methodology, or other factors.

- The data columns in the table can represent a range of possible issues associated with data in risk assessment, most often related to either the availability of the necessary data of the target metal for different types of national or regional risk assessments, or the availability of ancillary data at any scale that is necessary to appropriately determine risk.

6.3.5 Charge Question 3.5. Please comment on the objectivity of the Hard Soft Acid Base concept to applications of stability of metal complexes in <u>toxicity assessments</u>. See Section 4.1.2. (Emphasis added by SAB.)

6.3.5.1 Comments in Response to Charge Question 3.5

Although charge question 3.5 specifically seeks comments on the objectivity of the Hard Soft Acid Base (HSAB) concept to applications of stability of metal complexes in toxicity assessments, the SAB finds that the question could also apply more generally to risk assessment. The SAB has commented on the objectivity of HSAB regarding both toxicity assessments and the broader issue of risk assessment.

The SAB concludes that the application of the Hard Soft Acid Base (HSAB) concept to the stability of metal complexes in the context of <u>*risk assessment*</u> is generally presented in an unbiased manner, with perhaps one possible exception. General statements that hard acids are more toxic than soft acids should be worded more carefully to ensure that the statements are not interpreted in a broader context than warranted by the available data.

The application of the HSAB concept specifically to <u>*toxicity assessment*</u> is a more complex issue. Whereas the HSAB concept is generally useful for assessing the strength of binding of a metal to a receptor (if the chemical structure of the receptor is known), the extent of the toxic response once the metal is bound is not really addressed by the HSAB concept. Clarification of this distinction would improve the objectivity of this section of the Framework.

The clarity and completeness of the presentation could be improved by expanding the introduction with the following context for the application of the HSAB concept. The HSAB concept is a valuable way to summarize a considerable amount of qualitative chemical information and to allow the user to develop an intuitive feel for which complexes are likely to be more and less stable. The concept is well established in mainstream chemistry. However, the user should be aware that, while HSAB is useful for qualitative assessments of complex stability, quantitative calculations still depend on thermodynamic data such as stability constants and solubility products. These thermodynamic data are the basis of the models of metal speciation. The SAB also notes that additional citations to applications of the HSAB concept in environmental science would be useful (e.g., Sposito, 1989). In addition, the SAB recommends that, to ensure the accuracy of the presentation, the solubility constants in the Framework should be checked against established compilations of data.

6.3.5.2 Key Recommendations in Response to Charge Question 3.5

Short-term

1. General statements indicating that hard acids are more toxic than soft acids should be worded more carefully to ensure that such statements are not interpreted in a broader context than warranted by the available data.

2. The Framework should indicate that the HSAB concept does not address the extent of the toxic response of a metal once it is bound to a receptor. The HSAB concept is generally useful for assessing the strength of binding of a metal to a receptor. However, the extent of the toxic response once the metal is bound is not really addressed by the HSAB concept.

3. The introduction to the HSAB discussion should be expanded to make users aware that while HASB is useful for qualitative assessments of complex stability, quantitative calculations still depend on thermodynamic data.

4. Additional citations to applications of the HSAB concept in environmental science should be included in the Framework.

5. The solubility constants in the Framework should be checked against established compilations of data.

6. Specific revisions provided in Appendix C of this report should be incorporated into the Framework to improve the clarity of the HSAB discussion.

6.3.6 Charge Question 3.6. Please comment on the objectivity of the atmospheric metal chemistry discussion and its application to exposure assessments. See Sections 3.3.1.1 and 4.1.7. (Emphasis added by SAB.)

6.3.6.1 Comments in Response to Charge Question 3.6

In responding to this charge question, the SAB notes that none of the Metals Risk Assessment

Framework Review Panel members has an active research program in atmospheric chemistry. The SAB therefore recommends that an atmospheric chemist review these sections of the Framework to ensure that there are no gaps in coverage, beyond those cited below.

The SAB notes that there is no recommendation in Section 3.3.1.1 specifically addressing *exposure assessment*. The one bulleted recommendation in Section 3.3.1.1 addresses models for metal speciation in the atmosphere, and there is no text in Section 4.1.7 of the Framework to support that one recommendation. The rest of the text in Section 3.3.1.1 is a summary of some of the key points of Section 4.1.7, but it is not cast in the form of a recommendation.

Section 4.1.7 of the Framework describes metals adsorbed to particles as the principle route of *direct* exposure to metals in the atmosphere and cites the importance of particle size in transport and exposure. The SAB concurs, within the limits of our knowledge of the subject, that this assessment of *direct* exposure is generally accurate for most metals. However, the discussion of atmospheric chemistry and its application to exposure assessment would be more complete if the following issues were addressed.

- A statement should be included about the potential for longer-scale transport of metals from a source through the atmosphere to soil, water, or air, from which exposure ultimately occurs. Even if the process for metals follows principles already established and described for organic compounds, and EPA does not want to repeat that description in the Framework, a statement about the similarities and differences between inorganic and organic compounds would improve the completeness of the Framework. For example, while many metals are transported in the atmosphere primarily only on the surfaces of particles, many organic compounds are transported in the atmosphere primarily as a component of the vapor phase.

- A statement about the potential importance of volatile inorganic species of metalloids (e.g., $H_2S(g)$, $AsH_3(g)$) should be included in the atmospheric chemistry discussion.

- A statement about the potential importance of atmospheric transport to "background" concentrations of metals in the environment should be included either in the section of the Framework discussing atmospheric chemistry or in the "background" section.

6.3.6.2 Key Recommendations in Response to Charge Question 3.6

Short-term

1. Because none of the Metals Risk Assessment Framework Review Panel members has an active research program in atmospheric chemistry, an atmospheric chemist should review Sections 3.3.1.1 and 4.1.7 of the Framework to ensure that there are no gaps in coverage beyond those identified below.

2. Section 3.3.1.1 of the Framework should contain a recommendation specifically addressing exposure assessment.

3. The Framework should include a statement addressing the potential for long-scale transport of metals from a source through the atmosphere to soil, water, or air from which exposure ultimately occurs.

4. The atmospheric chemistry section of the Framework should contain a statement concerning the potential importance of volatile inorganic species of metalloids (e.g., $H_2S(g)$, $AsH_3(g)$).

5. The Framework should contain a statement concerning the potential importance of atmospheric transport to "background" concentrations of metals in the environment.

6.3.7 Charge Question 3.7. Please comment on the objectivity of the metal chemistry and environmental parameters incorporated in the various metal surface complexation and partition coefficient models and their applications to exposure assessments. See Sections 3.3.1.2 and 4.1.4.1.

6.3.7.1 Comments in Response to Charge Question 3.7

The SAB finds the Framework discussion of surface complexation and partition coefficient models to be generally accurate and unbiased, but notes the following areas where the presentation seems to lack completeness.

- The limitations of the models, particularly the data needs for the surface complexation models and the potential difficulty of obtaining the data, should be made more clearly obvious. The SAB questions, for example, how realistic it is to propose routine application of surface complexation models in risk assessment.

- A statement should be made in the Framework about the importance of balancing detail and uncertainty over the entire assessment. The SAB questions, for example, whether it is appropriate to combine a detailed, molecular-level model of one process with an empirical, "black-box" model of another process, within the same risk assessment.

- A statement should be made in the Framework about the applicability of the surface complexation and partition coefficient models as a function of ionic strength, particularly with regard to estuarine and marine environments.

- The sediment chemistry and soil chemistry sections of the Framework should be coordinated to ensure that similar recommendations are given for similar circumstances. Combination of the text addressing environmental chemistry of soils and sediments into a single section should be seriously considered (whereby it is recognized that ecotoxicity in the two environments should still be treated separately.)

- A statement should be made in the Framework to the effect that, if a K_d partitioning model is ultimately used, one should still be aware of factors considered in more detailed models. It is important to ensure that all relevant factors on which K_d depends (e.g., pH, etc.) have been appropriately considered; information should be given on how to test applicability of a K_d model. The usefulness of surface complexation modeling in

evaluating the potential variability of K_d for a specific situation should be noted.

- Emerging alternatives to the surface complexation models and K_d models should be mentioned in the Framework. Alternatives include distributed ligand models, which are similar to WHAM.

6.3.7.2 Key Recommendations in Response to Charge Question 3.7

Short-term

1. The limitations of the models discussed in the Framework, particularly the data needs for the surface complexation models and the potential difficulty of obtaining the data, should be more clearly articulated.

2. The Framework should contain a discussion concerning the appropriateness of combining detailed models with more uncertain models in the same risk assessment.

3. The Framework should contain a statement about the applicability of surface complexation and partition coefficient models in estuarine and marine environments as a function of ionic strength.

4. The sediment chemistry and soil chemistry section of the Framework should provide similar recommendations for similar circumstances.

5. The Framework should contain a statement indicating that if a K_d partitioning model is used, one should still be aware of factors considered in more detailed models.

6. The Framework should discuss distributed ligand models as emerging alternatives to surface complexation models and K_d models.

6.3.8 Charge Question 3.8. Please comment on the objectivity of the discussion and recommendations on natural background of metals. See Sections 3.1.2.1 and 4.2.2.1.1).

6.3.8.1 Comments in Response to Charge Question 3.8

The SAB finds that a number of revisions are needed in the section of the Framework that discusses natural background levels of metals. Revisions are needed to improve clarity and completeness of the section. The SAB strongly recommends that the EPA use the term "ambient" or "ambient levels" in the Framework rather than "background," both in the glossary and throughout the text and recommendations. The following changes should be made in the glossary.

Glossary recommendation:

1. Delete the term – "Background"
2. Add – "Ambient Levels": The amounts of metals occurring in soil, water, sediment, or air that represent the combined contributions from natural and various anthropogenic sources. These ambient levels may be highly region-specific but can be used as a

baseline against which elevated levels from other natural or anthropogenic sources can be compared.

The term background is often incorrectly assumed to connote "natural" and therefore "safe" or of no significant human or ecological health concern. However, ambient levels can vary, or can be inherently high enough to represent a potential health concern in and of themselves. They can also represent a total level from a combination of natural and anthropogenic sources, some of which may be historical or unknown. For metals in particular, the concept of background levels is complicated by several factors, as described in the Framework document, which include the sometimes highly variable natural levels of metals in soils, sediments, air and water, various historical anthropogenic sources or activities, and air deposition from distal anthropogenic sources.

For example, natural levels of arsenic in soils can vary over a wide range from region to region depending on the sediment types from which the soils are derived, by as much as a factor of 10- to 20-fold. In addition, arsenical pesticides have been used over the past hundred years in agricultural and other settings; smelting and other air emissions can also contribute to local arsenic soil levels. Also, certain conditions, such as the chemistry of landfills, can lead to mobilization and release of natural sources of arsenic from rocks and soil, leading to greatly elevated arsenic levels in groundwater, but from entirely natural sources of arsenic. However, this can be distinguished from normal ambient levels with appropriate sampling and/or modeling. Use of the term "ambient" does not connote an ability to identify the various contributions from natural and anthropogenic sources, but does distinguish between setting a benchmark level for a site or region against which other anthropogenic or anthropogenically-influenced inputs of concern can be measured. Anthropogenic metals can be those that are released into the environment from a specific human activity (i.e. a point source emission) or "natural" metals that may move from one environmental compartment to another (i.e. soil to groundwater) due to a change in environmental chemistry related to a human activity.

Since the concept of "background" is even more difficult to characterize in a human context, the SAB recommends defining and using the term "body burden" in this instance, since it is also a neutral term that attempts to quantify an individual's steady-state level using biomonitoring of one or more sample matrices (for example, blood, urine, hair, toenails, bone scan, etc.). The Centers for Disease Control's (CDC) National Health and Nutrition Examination Surveys (NHANES) study is currently attempting to quantify and characterize body burdens in individuals so as to develop a national database that can serve as the equivalent of a baseline measure against which the levels in an individual can be compared. Section 4 of the Framework currently does not discuss this important issue. The SAB therefore recommends that the following definitions be added to the glossary and discussed in new sections in the human health effects parts of Section 4.

Glossary recommendation:

1. Add – Body Burden: An estimate of the concentration(s) of a metal or metal species in specific tissues or the entire body, determined by the use of biological monitoring data in the appropriate matrix.
2. Add – Human Biological Monitoring: Use of measurements in specific tissues or matrices

(blood, urine, hair, toenails, bone, etc.) of specific metals or metal species in order to assess exposure or estimate body burden.

The SAB also finds that Section 4 of the Framework does not adequately describe biomonitoring. This is an important emerging area of public health evaluation and exposure assessment that should be addressed. As with other aspects of metals analysis, speciation, method of analysis, and choice of the appropriate matrix are critical aspects of effective biomonitoring in humans. For example, analysis of chromium in blood, serum or urine does not provide a way to distinguish between nutritional forms of chromium from food or supplements versus environmental or occupational exposures to hexavalent chromium that may be of concern. Likewise, analysis of total arsenic in blood or urine does not reflect body burdens or recent exposures to inorganic arsenic since food contains high but variable levels of organic arsenic forms. However, arsenic in toenails provides both specificity for inorganic arsenic and an integration of arsenic exposures and steady-state levels over several weeks or months of exposure. Thus, metal-specific issues need to be considered for any biomonitoring program. However, effective biomonitoring can provide excellent data on individual body burdens that may reflect both exposures of concern and potential health risks. The lack of discussion on this topic is a serious deficiency of both Sections 3 and 4 of the Framework. The SAB strongly recommends amending these sections to include this discussion, and further recommends that the EPA consider partnering with CDC through its ongoing NHANES and State pilot biomonitoring programs in this important area.

6.3.8.2 Key Recommendations in Response to Charge Question 3.8

Short-term

1. EPA should use the term “ambient” or “ambient levels” in the Framework rather than “background” both in the glossary and throughout the text and recommendations. This is a strong recommendation of the SAB. A recommended definition of “ambient levels” is provided in the detailed comments above.

2. The term “body burden” should be defined and added to the Framework to describe the concentration(s) of a metal or metal species in specific tissues or the entire body, determined by the use of biological monitoring data in the appropriate matrix.

3. The term “human biological monitoring” should be defined and used in the framework glossary and text. A recommended definition is provided in the detailed comments above. The Insititute of Medicine of the National Academies of Science has completed a substantial amount of work in this area (National Academies of Science, 2004).

Long-term

4. The SAB recommends including a discussion of the topic of biomonitoring in Sections 3 and 4 of the Framework, and also recommends that EPA consider partnering in biomonitoring efforts with the Centers for Disease Control through ongoing National Health and Nutrition Examination Surveys (NHANES) and state pilot biomonitoring programs.

6.3.9 Charge Question 3.9. Please comment on the objectivity of the discussion of essentiality versus toxicity, including the relationship between Recommended Daily Intakes (RDAs) and thresholds such as Reference Doses (RfDs) and Reference Concentrations (RfCs). See Sections 3.1, 4.3.2, and 4.3.3

6.3.9.1 Comments in Response to Charge Question 3.9

The SAB finds that a number of revisions are needed in the Framework to clarify and ensure accuracy of the discussion of essentiality, Recommended Daily Intakes, and thresholds such as Reference Doses and Reference Concentrations. The SAB provides the following comments and recommendations in response to charge question 3.9.

- The SAB notes that for some metals, there might be an apparent discrepancy between the RDA and the calculated RfC or RfD. The EPA should consider the RDA for essential metals when considering the RfC/RfD. However, it should be noted that the RDA is usually satisfied by normal dietary intake of food, so that the RfC/RfD may be defined as a potential increment to the body burden of that metal from other dietary or extrinsic sources.

- The SAB notes a need to define essentiality and, in this definition, to include the role of the metal in an essential physiological or biochemical process.

- The SAB notes that in Section 4.3.2 of the Framework it is important to restrict the discussion of essentiality to humans and to revise tables 2-1 and 4-12, which are identical. Table 2-1 could include a list of essential and non-essential metals in all organisms, with footnotes to denote those known to be essential in just plants, animals or humans. Table 4-12 should be restricted to a list applicable solely to humans.

- The SAB notes that the current versions of Tables 2-1 and 4-12 need major revisions. The following recommendations apply specifically to the human table. It is recommended that Mg be added to the list of nutritionally essential metals. In addition, the middle column of the table should be eliminated and the metals in that column moved to the third column that lists metals with no known beneficial effects. The metals in the second column that should be moved to the third column include: As, B, Ni, Si, V, Ba, and Sr. These particular metals should be noted by asterisks in the third column to denote that there are limited human data for these metals.

- The SAB notes that a summary table should be added that includes RDA, RfDs, and RfCs available for the essential metals. The table should also include the adverse effects that occur at concentrations near or below the RDA for a given metal. This section should also specifically reference recent U.S. Department of Agriculture (USDA) and National Research Council (NRC) reviews on essentiality of elements in humans.

6.3.9.2 Key Recommendations in Response to Charge Question 3.9

Short-term

1. The term, "essentiality" should be defined in the Framework. The definition should address the role of the metal in essential physiological or biochemical processes.

2. The discussion of essentiality in the Framework should be limited to humans. Table 2-1 could include a list of essential and non-essential metals in all organisms, and Table 4-12 could include those applicable solely to humans.

3. The major the revisions of Tables 2-1 and 4-12 discussed in the detailed comments above should be incorporated into the Framework.

Long-term

4. The Framework should be revised to consider the Recommended Daily Intake for essential metals when considering Reference Doses and Reference Concentrations.

5. The Framework should contain a summary table providing Recommended Daily Intakes, Reference Doses, and Reference Concentrations for essential metals. The table should also include adverse effects that occur at concentrations near or below the Recommended Daily Intake for a given metal.

6.3.10 Charge Question 3.10. Please comment on the objectivity of the discussion and recommendations presented for assessing toxicity of mixtures, including how to assess additivity versus departure from additivity (See sections 3.1.3.4 and 4.3.6).

6.3.10.1 Comments in Response to Charge Question 3.10

The SAB finds that a number of revisions are needed in the discussion of toxicity of mixtures that is contained in the Framework. The SAB provides the following specific comments and recommendations in response to charge question 3.10.

- The SAB finds that the Framework discussion of the mixtures topic (Section 4.3.6) is limited and needs clarification and expansion. This section needs to be expanded to address co-exposures with organic pollutants (e.g., TCE, solvents, hydrocarbons) and air pollutants (e.g., gases such as ozone and particulates). The section needs more and improved examples of interactions for each of the conditions, and would benefit from a table that lists typical interactions and the ensuing effects on toxicity.

- The SAB recommends that the example of the selenium and mercury interactions on the bottom of page 4-78 be deleted. It is not an appropriate example since it leaves the impression that selenium supplementation should be used to prevent mercury toxicity.

- The SAB recommends that the mixtures topics part of the Framework (currently Section

4.3.6) contain subsections:
a.) Exogenous non-essential metal(s) effect on nutritionally essential metals.
    i) effects via molecular/ionic mimicry
b.) Interactions between non-essential metals
    i) effects via interactions at a common site
    ii.) effects via one metal affecting one site and another metal affecting another site
c.) Interactions of metals with non-metals
    i.) interactions with organics
        1) effects on toxicity of the metals
        2) effects on toxicity of the organics
    ii.) interactions with gasses and/or particulates
        1) affecting metal uptake
        2) affecting metal toxicity

- The SAB suggests the inclusion of a new Framework recommendation that states: "Metal mixture interactions and toxicity need to be clearly demonstrated by the use of:
  a.) proper experimental design (National Research Council, 1988)
  b.) appropriate plotting of diagrams
  c.) rigorous statistical evaluation to demonstrate synergy, additivity, potentiation, sub-additivity and/or antagonism."

- The recommendations in Section 3.1.3.4 of the Framework need to address the National Academy of Sciences/National Research Council (NAS/NRC) *Complex Mixtures* report (National Research Council, 1988). Recommendation 1 (page 3-9, line 9) in Section 3.1.3.4 should address the NRC report. Recommendation 4 (page 3-9, line 22) in Section 3.1.3.4 should be rephrased to state: "There are established interactions that are based on metal mimicry. Future research goals should determine how considerations of metal mimicry affect risk assessments and metal toxicity."

- A definition of metal mimicry is needed in the glossary of the Framework. The SAB suggests the following definition: "Metals that exhibit structural similarity which results in competition for essential receptors thus disrupting normal functions, such as chromate or arsenate substituting for sulfate or phosphate, lead replacing Ca or Zn, and Cd substituting for Zn or Ca." It might also be helpful to include in Section 4 of the Framework a table that presents examples of well-established metal mimicry. It is also important to note that metals can profoundly influence each other's biology through mechanisms other than mimicry.

6.3.10.2 Key Recommendations in Response to Charge Question 3.10

Short-term

1. Section 4.3.6 of the Framework should be expanded to address co-exposures with organic pollutants (e.g., TCE, solvents, hydrocarbons) and air pollutants (e.g., gasses such as ozone and particulates). More and improved examples of interactions for each of the conditions and a table listing typical interactions and effects on toxicity should be included in this section of the

Framework.

2. The example of selenium and mercury interactions on the bottom of page 4-78 of the Framework should be deleted, because it leaves the impression that selenium supplementation should be used to prevent mercury toxicity.

3. Additional sections (listed in the detailed comments above) should be included in the mixtures topics part of the Framework.

4. A new recommendation should be included in the Framework stating that metal mixture interactions and toxicity need to be clearly demonstrated by the use of: proper experimental design, appropriate plotting of diagrams, and rigorous statistical evaluation to demonstrate synergy, additivity, potentiation, subadditivity, and/or antagonism.

5. Section 3.1.3.4 should be revised to address the National Academy of Sciences/National Research Council complex mixtures report (National Research Council, 1988).

6. A definition of metal mimicry (provided in the detailed comments above) should be included in the glossary of the Framework. A table in Section 4 of the Framework should contain examples of well-established metal mimicry.

6.3.11 Charge Question 3.11. Please comment on the objectivity of the discussion and recommendations concerning natural background, bioavailability, bioaccumulation, biomagnification, and trophic transfer in both aquatic and terrestrial environments. See Sections 3.2.2 to 3.2.4, 3.3.2, 4.4.3, 4.5.4, and 4.5.6 to 4.5.9.

6.3.11.1 Comments in Response to Charge Question 3.11

The SAB finds that many aspects of the discussion in Sections 3 and 4 of the Framework are objective and of reasonable utility for risk assessors. The level of detail seems appropriate for a document of this type (i.e., screening level guidance document). However, as discussed above, there are parts of the document that could be improved and there are issues of balance among parts of the document that should be addressed. For example, the discussions of bioaccumulation, biomagnification and trophic transfer are confusing at times. Some of the recommendations in Section 3 are inconsistent with the discussion in Section 4 and the issue papers. The Framework brings up some very important issues reasonably well. But it also seems to advocate some methods without reflecting important uncertainties, unknowns, or lack of informed consensus in their base of scientific support. After revisions, the greatest utility of the Framework will be its value as a statement of considerations unique to metals. The major issues that should be addressed lie in: the need for balance in integrating sections, the imbalance among recommendations, the need to integrate discussions of uncertainties, and some omissions.

Routes of Exposure

The SAB notes that the discussion of dietary exposure and trophic transfer in Section 4 of the

Framework was not reflected in Section 3. Section 4.4.2.3 of the Framework discusses limitations to the SEM-AVS approach that are not mentioned in Section 3 (see details below). Both sections appear to be more conciliatory than analytical. The statement that "the most widely used approach of assessing metal exposure in sediments is based upon EqP theory" is not true. Many more agencies and scientists use the methods detailed in documents referenced by National Oceanic and Atmospheric Administration (NOAA) and/or Canadian guidelines (Long & Morgan, 1990; 1991; McDonald et al, 1996; McDonald et al., 2000). These methods and concepts are discussed in the Chemistry section, but not mentioned in Section 4.4.2.3.

Natural Background

In the Framework, "background" is defined as both natural and anthropogenic levels of metal. This lack of clear definition confuses the issue. As discussed in the response to charge question 3.8 above, natural background should be a consideration, but the Framework document treats it as a non-issue. In the Framework discussion of background, no medium (e.g., soil, sediment, water) is specified but the issue of background is different in different media. This issue is acknowledged to be complex when evaluating sediments if particle size is ignored and no sediment cores are available. The Framework states that background concentrations can vary by as much as five orders of magnitude. The SAB finds that five orders of magnitude variation in metal concentration is most likely an exaggeration when described in reports and literature. In part, large variances may be the result of using earlier sediment and water chemistry data, when adequate" clean chemistry" methods were not used. Mention of the EPA Storage and Retrieval (STORET) database, with a caveat about quality assurance, does little to help the risk assessor. STORET contains data that could be incorrect by five orders of magnitude because it represents earlier, non-clean chemical analyses. The Framework needs to emphasize the importance of ultra-clean chemistry in determining all metal concentrations, but especially those values that might be background.

In the response to charge question 3.8 above, the SAB recommends that the EPA use the term "ambient" or "ambient levels" rather than "background." However, the Framework document should distinguish between "natural" and higher-level anthropogenically-induced backgrounds. In discussing ambient or background levels, the Framework needs to specify the need for determining what background is and, consequently, what to consider. Using the term "natural" likely complicates the task of defining a base concentration for comparison in metal risk assessment. The Framework should provide guidance to establish an ambient or "background" concentration that would be operationally defined for the assessment taking into consideration realistic concentrations that often will reflect both natural and anthropogenic influences. Acknowledging "background" concentrations becomes assessment-specific. For example, San Francisco Bay sediments have high nickel concentrations stemming from historical times. Arsenic at regional scales presents a similar situation. Background concentrations ultimately dictate the kinds of organisms, the nature of ecology, and types of chemistry at that site or region.

Bioavailability

Bioavailability is a useful concept and should be brought into the Framework

recommendations. The Framework statement on the "bioavailable fraction" is very important, both in terms of the science and moving the Framework forward. The Framework document does handle the concept of bioavailability more extensively than other aspects. It is clear that in the view of the document "bioavailability" concerns speciation and other water chemistry effects. "Trophic transfer," "dietary exposure," and "biomagnification" are mentioned in a few places, but there is little in Section 3 of the Framework to help the risk assessor understand and employ these concepts. The discussion of dietary toxicity leaves out important examples and understates the importance of this route of exposure, as well as the increasing knowledge of it. As the SAB has previously noted (U.S. EPA SAB, 2000a), dietary exposure is an important consideration, or at least uncertainty, in any assessment of the ecological risks of metals. The Framework does not adequately integrate this uncertainty into the overall view it presents to risk assessors. There is no integrated view of how an organism might respond to all sources in different circumstances; the routes of exposure are treated as if they are not related.

A problem associated with the hazard assessment of metals in water is that very small deviations from background concentrations result in very large amplification through the environment because of high K_ds and relatively high BCF/BAFs for many metals. No guidance concerning this issue is provided in the Framework document, nor is the essence of the issue discussed at any length. Bioavailability as shown in the conceptual model in the Framework should include both exposure and dietary uptake. The Framework text provides an uneven approach and should be expanded to address the influence of dietary uptake. The conceptual model in Figure 2-2 of the Framework includes dietary uptake, as it should, and provides a rationale for including food type and food choice. However, there is also an ecological need to incorporate dietary uptake into the Framework discussion. There should be an emphasis in the Framework on the need to understand species presence and the nature of the food web. Trophic transfer, for example, has been shown to be an important route of uptake of metals from sediments into fish via planktonic invertebrates and into epibenthic invertebrates feeding on periphyton.

Bioaccessibility

The SAB finds that "bioaccessibility" is properly considered in the document and represents the labile portion of the metal.

Bioaccumulation

Bioaccumulation is a concept that is different from biomagnification. This presents some level of confusion in the discussion of the different levels of risk assessments in the Framework. The important point that should be made in the Framework is that metals bioaccumulate, and trophic transfer is important. It is less important that biomagnification through the food web is likely to occur only in some circumstances (although examples exist for selenium and methylmercury).

Bioaccumulation should be reviewed in the Framework as a concept for use in risk assessments, particularly in the site-specific risk assessments. The issue of what construct to use to express bioaccumulation (e.g., BCF, BAF, models) is separate from consideration of the

bioaccumulation processes. Sections 3 and 4 of the Framework place great emphasis on the limits of a ratio approach and little emphasis on bioaccumulation processes that are relevant to exposure analysis in a risk assessment. A concern of the SAB is that coefficients in the ratios are not independent of exposure concentrations. The coefficients are calculated and used but they are highly variable. The concept of using BAF or BCF ratios can be appropriate, but it should never be assumed that they are constant(s), as is the typically assumed in uses like hazard assessment. This issue is further discussed in the response to charge question 3.12 below. The SAB recommends that a text box be included in the Framework document to highlight concept of BCF versus the use of this as a tool in site specific or national assessments. The SAB also finds that there is a strong need for presentation of a conceptual model of bioaccumulation in the Framework. Such a conceptual model should tie bioaccumulation to toxicity. If bioaccumulation and bioconcentration factors are treated more comprehensively, the Framework will be a more cohesive document. The SAB's discomfort with the treatment of BCF and BAF has to do with difficulties in measuring bioaccumulation, which involves estimates of uptake, depuration, etc. Any method that can be related to a dynamic intake, and that relates site of target toxicity with effects, would be of value. Such models need to be better incorporated into the bioaccumulation discussion in the Framework. Until this information is incorporated into the document, toxicity tests will be utilized, or concentrations in tissues will be used, without any understanding.

Essentiality

The SAB finds that the discussion of essentiality in the Framework also needs to be expanded, particularly with regard to how essentiality influences accumulation factors. Tissue concentrations can vary by a large amount and there is a need to discuss the factors influencing the site-specific characteristics that lead to a given BCF. In this regard the Framework document should discuss the state of the science (versus what might simply be included in a Framework).

Concentrations in "Metallo-regions"

The SAB recommends using a geometric progression (log-normal distribution) for metal concentrations in either "metallo-regions" or catchment basins and describing the low-end of the distribution (e.g., 95^{th} or 90^{th} percentile exceedence zones) as potential problem areas. In a national or ranking risk assessment, a conservative approach would need to be taken by using medians and the 90^{th} (or so) percentile. For national-level risk assessments, one would necessarily want to err on the side of conservatism.

Critical Body Residues

The SAB finds that the concept of critical body residues (CBR) is handled unevenly in the Framework and is over emphasized. The fact that CBR can be measured does not necessarily mean it is the concentration at the site of toxic action. Further, there are few data on this and it has been measured in only a few species. The concept may be an idea that can be used in the future.

Acclimation

The SAB notes that there is much discussion in the Framework of acclimation and adaptation. The costs of adaptation are discussed well in Section 4, but that discussion does not appear to carry over to section 3. It is well known that organisms have developed a variety of physiological and/or biochemical strategies for dealing with metals exposure due to the ubiquitous presence of metals in the natural environment. In many cases these strategies have permitted organisms to survive and thrive in areas where they would not normally be able to exist. The importance of considering these strategies has long been debated among the regulatory and regulated communities. It is also true that many metals are essential for the health and development of organisms, and in some cases it has been observed that organisms used in toxicity tests that have been cultured in "metals-deficient" media have been shown to be more sensitive to subsequent metals exposure than are wild organisms raised in natural environmental conditions. The general recommendation that has come from the scientific community is that researchers should ensure that organisms used in conducting toxicity tests are cultured (or at least acclimated for a period of time) to test media that contain metals concentrations that are "similar" to natural background concentrations, not concentrations similar to the site in question. It is assumed that this approach will reduce the potential of overestimating toxicity from "metals-deficient" stressed organisms, while ensuring that underestimations of toxicity are not reached from tests conducted with "metals-acclimated" organisms. To this end, it is equally important that risk assessors are mindful of this potential concern and consider it in conducting their evaluation of effects data. The SAB finds that the discussion and recommendations contained in Sections 3 and 4 relative to this issue do not adequately describe and delineate the difference between true metals acclimation and test organism stress due to metals deficiency.

6.3.11.2 Key Recommendations in Response to Charge Question 3.11

Short-term

1. In addition to the discussion of EqP-based methods for assessing metal exposure in sediments, Section 4.4.2.3 of the Framework should contain a discussion of other methods (referenced above) for assessing metal exposure in sediments.

2. The Framework should emphasize the importance of ultra clean chemistry in determining all metal concentrations, but especially those values that might be "ambient" levels. As discussed in the response to charge question 3.8, the Framework does not provide a clear definition of "background" levels of metals, and the SAB recommends using the term "ambient" or "ambient levels" rather than "background."

3. The Framework should distinguish between "natural " and higher-level anthropogenically-induced ambient concentrations of metals, and provide guidance to establish an ambient or "background" concentration that would be operationally defined for an assessment, taking into consideration realistic concentrations that often will reflect both natural and anthropogenic influences.

4. The concept of bioavailability should be brought into the Framework recommendations. The Framework should provide information to help risk assessors understand and employ the

concepts of “trophic transfer, “dietary exposure,” and “biomagnification.”

5. The Framework text should be expanded to address the influence of dietary uptake of metals. There is an ecological need to incorporate dietary uptake into the Framework discussion.

6. Bioaccumulation should be reviewed in the Framework as a concept for use in risk assessment, particularly site-specific risk assessment. A text box should be included in the Framework highlighting the BAF or BCF ratio concept versus its use as a tool in site specific or national risk assessments.

7. The discussion of essentiality in the framework should be expanded, particularly with regard to how essentiality influences accumulation factors.

8. EPA should use a geometric progression (log-normal distribution) for metal concentrations in either “metallo-regions” or catchment basins and describing the low end of the distribution as potential problem areas.

10. The Framework should be revised to state that, although critical body residues can be measured, they do not necessarily reflect concentration at the site of toxic action. The Framework should also indicate that critical body residues have only been measured in a few species. The SAB notes that the concept of critical body residues is handled unevenly in the Framework and is over emphasized.

11. The discussion and recommendations in Sections 3 and 4 of the Framework concerning acclimation and adaptation should be revised to describe and delineate the difference between true metals acclimation in test organisms and test organism stress due to metals deficiency.

6.3.12 Charge Question 3.12. Please comment on the objectivity of the framework statement that the latest scientific data on bioaccumulation do not currently support the use of bioconcentration factor (BCF) and bioaccumulation factor (BAF) values as generic threshold criteria for hazard classification of inorganic metals (see recommendation on page 3-17, lines 27-29 of the document). By this, the framework means that various assumptions underlying the BCF/BAF approach, including the independence of BCF/BAF with exposure concentration and the proportionality of hazard with increasing BCF/BAF do not hold true for the vast majority of inorganic metals assessed. Please comment on the framework's acknowledgement that the appropriate use of BCFs/BAFs to evaluate metal bioaccumulation, including the degree to which BCFs/BAFs are dependent on exposure concentrations, needs to consider information on bioaccessibility, bioavailability, essentiality, acclimation/adaptation, regulation of metals (uptake and internal distribution), detoxification and storage, dependence on exposure concentration, and background accumulation. While the ability to quantitatively address all these factors may be limited at the present time, the framework states that their potential impacts should at least be qualitatively addressed. See Sections 3.2.4, 3.3.2.5, and 4.5.8.

6.3.12.1 Comments in Response to Charge Question 3.12

The SAB agrees with the statement that BCF/BAFs do not apply for metals. The language of the Framework is useful in describing the context of use for BCF/BAF. As stated in the Framework, it is appropriate largely for use in a site assessment. The Framework acknowledges that these methods may not be the best approach for use in a national assessment, and especially for hazard rankings. However, guidance is offered in the Framework on how to derive BCFs/BAFs (e.g., pages 3-17, and 3-33). The SAB finds that the Framework document needs a clearer discussion of when to use these tools, their deficiencies, and when they should not be used. The justification of why or why not to use them needs to be more explicit and coherent.

BCF/BAF

The SAB notes that the Framework does not mention that BCF/BAFs vary 50 fold or more for every metal, partly because of inherent biological diversity in response to metals. A careful analysis of the literature would show alternatives to the BCF/BAF approach that are much more flexible and less variable (e.g., biodynamic models).

The Framework correctly assesses the state of the science. Section 4.5.8 of the Framework clearly expresses the issues and identifies shortcomings of the BCF/BAF approach. There is a difference in the utility of the BCF/BAF approach for assessing the risks associated with organics and inorganics, and the Framework appropriately addresses these differences. The SAB supports the call for more data on bioavailability, acclimation, storage, metal regulation, and accumulation as modifiers of BCF or BAF. There is no doubt that better data on metal storage, disposition in the body, and consequent potential toxicity, will result in better predictions of risk. However, in some cases where data are limited, a precautionary stance of using potential BAFs might be called for and not simply ignored. For example, it would be much clearer if the Framework were to state that the BCF/BAF does not work for national assessments but it has value for site-specific assessments.

The Framework should specifically address the issue of hazard assessment and consider trophic transfer. The Framework needs to consider options beyond dissolved metals toxicity tests. In this regard, the SAB suggests considering options that address: 1) the potential for trophic transfer, and 2) the potential for transformation into bioavailable organometal compounds.

6.3.12.2 Key Recommendations in Response to Charge Question 3.12

Short-term

1. The Framework should contain a clearer discussion of when to use BCF/BAFs, their deficiencies, and when they should not be used. The justification of why or why not to use them should be more explicit and coherent.

2. Assessment options beyond dissolved metals toxicity tests should be discussed in the Framework. In this regard, the SAB suggests that EPA consider options that address the

potential for trophic transfer and the potential for transformation into bioavailable organometal compounds.

6.3.13 Charge Question 3.13. Given the variety of organism responses to inorganic metals exposure, based on factors such as bioaccessibility, bioavailability, essentiality, uptake/excretion mechanisms, and internal storage/regulation, as described in Section 3.2.4, the framework states that BAFs/BCFs should be derived using mathematical relationships that represent the concentration in the organism or tissue as a function of the bioavailable concentration in the exposure medium/media for each set of exposure conditions. Please comment on whether this is the best approach based on the current state of the science or if there are alternative approaches that are more appropriate that can be routinely applied. See Sections 3.2.4, 3.3.2.5, and 4.5.8.

6.3.13.1 Comments in Response to Charge Question 3.13

The SAB finds that the mathematical relationships representing the metals concentration in the organism or tissue as a function of the bioavailable concentration in the exposure medium/media for each set of exposure conditions seem appropriate. However, the SAB provides the following specific comments.

- Section 4.5.8 of the Framework indicates that steady-state conditions are often the primary concern in metals risk assessments, yet there certainly can be instances of non-steady state conditions being of primary concern (e.g. episodic hydrologic events and related metal mobilization). Further, if the recommendations to not apply BCFs and BAFs are supported, the SAB questions why recommendations to derive them are included in the Framework.

- The SAB finds that Sections 2 and 4.5.8.1 of the Framework clearly articulate issues surrounding the derivation and utility of BCF/BAFs for metals. For all of the reasons discussed in these sections, it appears that the concept of the BCF/BAF for metals holds little utility in assessing the environmental toxicity of metals in hazards rankings. One optimal approach (least uncertain) for deriving these values would be to use the tissue concentration at the site of action and to relate this to the best estimate of the biologically available metal. However, few data exist to allow derivation of such a value.

- The SAB notes that one aspect not mentioned in Section 3.3.2.5 of the Framework is the use of multi-species model ecosystems to verify BAF or BCF predictions. Often the results of such real-world situations are to modify the growth (hence uptake and effects of metals). The effective rate of uptake is very important, as the Framework states. Hence, BAFs are not necessarily of value, as equilibrium situations are rarely found. The ideal is to have concentration measures at site of action and in the surrounding environment, but adequate tools are not immediately and widely available. Thus, the utility of the current construct is limited. If the Framework were to include bioaccumulation dynamics, the variability would be narrowed. On a site-specific basis, the ratios are better used than in national assessments because variability may be less. For organics there are some well

known and accepted assumptions. For metals there is a large variability around the BCF/BAF estimates. However, there is little guidance as to "where to draw the line."

- The SAB strongly concurs that one cannot use a BAF or BCF ratio for national assessments or hazard ranking procedures. The SAB feels that a bioenergetics approach offers valuable potential for understanding metal accumulation from air, sediments, soils or water (Wang et al., 1996; Schlekat et al., 2002). In the interim, the Framework should address metals bioaccumulation empirically for site assessments. In the future, there should be a concerted attempt to generate data at the site of action (Escher et al., 2004).

6.3.13.2 Key Recommendations in Response to Charge Question 3.13

Long-term

1. The SAB strongly concurs that one cannot use a BAF or BCF ratio for national assessments or hazard ranking procedures for metals and recommends that in the long-term EPA should incorporate a bioenergetics approach into the framework. Such an approach offers valuable potential for understanding metal accumulation for air, sediments, soil or water.

6.3.14 Charge Question 3.14. Please comment on the objectivity of the information and recommendations pertaining to the use of the acid-volatile sulfide-simultaneously extracted metals (AVS-SEM) approach and the biotic ligand (BLM) model. Are additional recommendations warranted? If yes, what are they? See Sections 3.2.6, 4.4.2.3, and 4.5.10.

6.3.14.1 Comments in Response to Charge Question 3.14

It is the opinion of the SAB that the concepts of SEM-AVS and BLM are clearly on the agenda for adaptation into risk assessment. The Framework comprehensively describes the theory and evidence behind both methods. However, the discussion in the Framework is unbalanced throughout in comprehensively evaluating the practical and theoretical challenges and inherent limitations that have been encountered in implementing the use of SEM-AVS (Cantell, Burgess & Kester, 2002). The primary literature contains a number of questions that are relevant with regard to implementation of SEM-AVS in either risk assessment or regulation. The theory itself is attractive and a strong literature supports its effectiveness in the environment of the typical sediment bioassay. There is no question that sulfides are important in metal associations in anoxic sediments, or that sulfides control pore water metal concentrations in bulk sediments. The questions about implementation of the methodology lie in how the complex vertical gradients of sediments will be sampled, how stable SEM-AVS characterizations will be for a site, and/or whether an SEM-AVS characterization will hold for sediments that are moved during normal resuspension, flood or bed-load transport events. The SAB has provided similar comments in a review of EPA's *Integrated Approach to Metals Assessment in Surface Waters and Sediments* (EPA SAB, 2000a). Many such questions were also raised in a very important review of sulfide dynamics and its relationship to the stability of AVS in a cover article of Environmental Science and Technology (Morse & Rickard, 2004).

A second issue is that, although AVS controls bulk pore water concentrations, it does not control metal concentrations in what an animal eats. The literature that considers dietary bioaccumulation from sediments raises important issues with regard to the design of most sediment bioassay experiments: the living nature of sediments and how that affects bioavailability, and the biases that can occur in sediment bioassays of the type typically used for the AVS concept. These issues are not necessarily resolved one way or the other, but they are substantial and well enough documented that risk assessors must be made aware of the debate and be prepared to consider the pros and cons of the SEM-AVS method in a balanced way (Lee et. al., 1988; Lee & Luoma, 1998).

The BLM is in the relatively early stages of development and also has inherent limits. For example, the BLM: 1) has no dietary component; 2) has no chronic component; and 3) has no cross-species comparisons among differing mechanisms for binding and effects-level metal concentrations. Similar comments were provided in the SAB review of the Biotic Ligand Model of the Acute Toxicity of Metals (EPA SAB, 2000b) The published literature on animals other than trout and fathead minnow show simple, and not unexpected, correlations between toxicity test outcomes and metal speciation, in the guise of a biological model. The BLM definitely does account for speciation better than any methods to date; but the BLM does have limits at the present state of knowledge.

The information presented in the Framework regarding the use of the BLM and SEM-AVS approaches is appropriate and reflects the current state-of-the-science. It is, however, interesting that the use of techniques relating to bulk sediment concentrations are conspicuously absent, at least in terms of their applicability to large scale assessments. Methods such as sediment quality criteria (SQC), threshold effect level (TEL), and probable effect level (PEL) have a good role in conducting metals risk assessment, especially when data are not available to address metals sediment toxicity through methods such as SEM-AVS. Further, the implied lack of bioavailability of metals associated with sulfides has come into question (Lee et al., 2000). For risk assessments of a broader nature, e.g., at the national level, clearly the only viable approach to be implemented may be through the assessment of bulk sediment numbers.

The SAB notes that the future of toxicity testing is moving toward mechanistic approaches and the BLM approach is a step in the right direction. An important feature of the BLM is that it addresses the site of action. For chronic effects, BLM may not apply since site of effect may change with exposure time frame. The risk assessor has to be aware that there is not an available comprehensive tool and that there are limits to each approach. However, advances that move risk assessment toward consideration of bioavailable fraction, mode of action, and a mechanistic approach are steps in the right direction.

6.3.14.2 Key Recommendations in Response to Charge Question 3.14

Short-term

1. The Framework should be revised to provide a more detailed discussion of the practical and theoretical challenges and inherent limitations that have been encountered in implementing the use of SEM-AVS.

2. The Framework should be revised to provide a more detailed discussion of the inherent limits of the Biotic Ligand Model discussed above.

3. The Framework should present corresponding information on the practical challenges and inherent limitations of using bulk sediment chemistry assessment methods.

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Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1

Framework Section 3.1.1 - Fate and Transport.

- The fate and transport section (Section 3.1.1) of the human health risk assessment recommendations provided in the Framework currently refers to the ecological and environmental chemistry sections for recommendations in this area. The SAB finds that this is appropriate.

Framework Section 3.1.2.1 - Background.

- Recommendation 1 (page 3-3, line 9) in Section 3.1.2.1 regarding background exposures should be modified such that the word "ambient" replaces the word "background." In support of this word change, the following definition for the word "ambient" should be added to the glossary section:

  Ambient Levels: The amount of metals occurring in soil, water, sediment, or air that represent the combined contributions from natural and various anthropogenic sources. This ambient level may be highly region-specific but can be used as a baseline against which elevated levels from other natural or anthropogenic sources can be compared.

- Recommendation 2 (page 3-3, line 15) in Section 3.1.2.1 should be expanded by the addition of the following phrase: "It is also important to consider speciation of the metals wherever and whenever possible."

- The following additional recommendation should be included in this section: "Ranges rather than averages should be used in risk assessments, especially for site specific evaluations."

Framework Section 3.1.2.2 - Air Pathways and Inhalation Exposure.

- Recommendation 1 in Section 3.1.2.2 (page 3-3, line 32) should be revised. Particulate matter that is less than 2.5 micrometers in size ($PM_{2.5}$) and nanoparticles are now of critical concern for the exposure and delivery of metals to humans and should be added as separate entities at the end of this recommendation. Support for the recommendation in Section 3.1.2.2 to focus inhalation exposure only on the small particles (PM_{10}) is given in Atmospheric Behavior and Chemistry Section (4.1.7) where the long atmospheric lifetime of small compared to large particles in the atmosphere is discussed. In general, the section on atmospheric chemistry of metals is rather short and not comprehensive but it does support the recommendation. EPA may want to consider addressing in this recommendation other larger size classes that can be important for long range transport and subsequent adverse effects. However, these considerations were not addressed in Section 4. In order to do so, the discussion will have to be expanded.

- A new recommendation should be added regarding the need to consider other particle

characteristics in addition to size, such as surface properties, solubility, and particle chemistry. The characteristics of inhaled particles are critical determinants how they react with biological membranes and can affect the efficacy of the uptake of metals across those membranes.

- Another recommendation should be added to the Framework regarding the need to consider the biological effects associated with inhaled mixtures such as metals in combination with other airborne pollutants including gases such as ozone (which can alter the permeability of the cell membrane so as to increase metal uptake by the cells). In addition, particulate matter (PM) itself is a unique mixture of metals, other inorganic compounds such as sulfates, and organic compounds (e.g., PAHs) adsorbed onto solid carbon cores, and should be addressed as such.

- The SAB finds that recommendation 2 (page 3-4, line 1) in Section 3.1.2.2 is appropriate as written.

Framework Section 3.1.2.3 - Soil, Dust and Dietary Exposure Pathway.

- The first recommendation in this section should be deleted. Although of less concern than other exposure pathways, dermal exposure should be considered because of potential skin effects.

- Recommendation 2 (page 3-4, line 16) in Section 3.1.2.3 should be revised starting at line 20 (page 3-4) to read "consider dermal sensitization, contact dermatitis and other direct skin effects. For example, nickel and chromium are both common allergens in sensitized people (approximately 2-5% of the population for each metal), and arsenic can cause both local irritation as well as increased risk of cancer at sites of repeated high dose application. Although dermal exposure in general is of less concern for metals, the potential skin effects of some metals should be considered by the risk assessor in the overall health evaluation."

- Recommendation 3 (page 3-4, line 23) in Section 3.1.2.3 is acceptable to the SAB.

- Recommendation 4 (page 3-4, line 27) in Section 3.1.2.3 should be modified by deleting text starting on line 28 (page 3-4) at the semicolon to end of paragraph (line 31). The SAB suggests this modification because, depending on the exposure situation, specific metals/metal forms, skin conditions, and dermal effects can be an issue. Assessors should be aware of potential uptake of metals in specific forms (e.g., nanoparticles), potential uptake of metals via unique exposure conditions (e.g., bathing, showering, swimming), and the uptake of metals through damaged skin (e.g., irritated skin, sunburn). Co-exposures of metals with other toxicants can also affect dermal uptake. Dermal metal exposures can produce allergic dermatitis (e.g., chromium, nickel, gold), irritation (e.g., arsenic, chromic acid), and skin cancer (e.g., arsenic) under certain exposure conditions.

Framework Section 3.1.2.4 - Water Pathway and Oral Exposure.

- The SAB finds that recommendation 1 (page 3-5, line 12) in Section 3.1.2.4 is acceptable in its current form.

- Recommendation 2 (page 3-5, line 17) in Section 3.1.2.4 should be amended to read: "It is recommended that site-specific assessments use measured metal concentrations within water distribution systems and at the tap."

- Recommendation 3 (page 3-5, line 20) in Section 3.1.2.4 should be amended by changing the word "negligible" to "less important." The term "surface" should be deleted.

Framework Section 3.1.2.5 - Integrated Exposure Approaches.

- Recommendation 1 (page 3-5, line 35) in Section 3.1.2.5 should be amended to indicate that the Integrated Exposure Uptake Biokinetic (IEUBK) Model should be "considered" rather than "recommended" and should make use of all available site-specific data, in particular factors that may influence oral uptake such as nutritional status of the affected population.

- With regard to recommendation 1 in Section 3.1.2.5, the SAB finds that the IEUBK Model is not applicable for all metals and, thus, similar models should be developed for other toxic metals/metalloids of concern. This is a research need that could be identified in a separate "research needs" document.

Framework Section 3.1.2.6 - Bioavailability.

- The SAB finds that recommendations 1 , 2, and 3 (page 3-6, lines 19, 23, and 28) in Section 3.1.2.6 are acceptable in their current forms.

- The SAB finds recommendation 4 (page 3-6, line 32) in Section 3.1.2.6 to be acceptable in its current form for lead, arsenic and potentially other metals.

- The SAB suggests deletion of recommendation 5 (page 3-6, line 35) in Section 3.1.2.6. The SAB notes that this is actually a research need and not a recommendation. Research needs could be addressed in a separate document.

Framework Section 3.1.3.1 - Physiologically Based Pharmacokinetic (PBPK) and Pharamcodynamic (PBPD) Modeling.

- Recommendation 1 (page 3-7, line 16) should be amended by replacing "bone" with "storage compartments such as bone." This change de-emphasizes bone and makes a more general recommendation that encompasses other metals.

- Recommendation 2 (page 3-7, line 21) should be amended by deleting "and" on line 21 and adding "(4) bioavailability, and (5) routes of exposure" at the end of the sentence

(line 22, page 3-7). This change is necessary because these other important factors also need to be included. The SAB also recommends expansion of the discussion of PBPK and PBPD modeling in Section 4.2.6 to include these parameters. References cited in Section 4.2.6 are appropriate, but the specific information from these citations should be summarized and included in the section. For example, information from the O'Flaherty (1998) review article on metals PBPK modeling (cited on page 4-68 of the Framework) should be summarized.

- Recommendations 3 (page 3-7, line 24) and 4 (page 3-7, line 30) in Section 3.1.3.1 should both be deleted and the following new Recommendation 3 should be added: "Although there is a useful PBPK model for lead, similar models for other metals are lacking and need to be developed and validated."

Framework Section 3.1.3.2 – Essentiality.

The SAB accepts the recommendation in this section, but feels that additional material is needed in the introductory paragraph of the section. It should be stated in this section that, "for some metals, there may be an apparent discrepancy between the Recommended Daily Allowance (RDA) and the calculated Reference Concentration (RfC) or Reference Dose (RfD). The EPA should consider the RDA for essential metals when considering the RfC/RfD. However, it should be noted that the RDA is typically satisfied by normal dietary intake of food and water, and therefore the RfC/RfD value may still represent a potential additional body burden of that metal from other dietary or extrinsic sources." Phrased another way, RfD/RfC values are presented as increments to RDAs. The SAB also notes that there is a need for a definition of essentiality. This definition should address the role of the metal in an essential physiological or biochemical process.

Framework Section 3.1.3.3 - Toxicity Testing.

The SAB suggests the following changes to this section (page 3-8):

- The first sentence in this section (lines 9-12) should be changed to read as follows: "At least five metals are accepted as human carcinogens – arsenic, beryllium, cadmium, chromium (VI) and nickel."

- Recommendation 1 in this section (line 22) should be amended by adding "with particular attention to route of exposure, speciation and life stage." to the end of the sentence.

- Recommendation 2 (line 26) in this section should be amended by adding, "with particular attention to route of exposure, speciation and life stage." to the end of the sentence.

- A new recommendation should be added to this section stating that, "Animal models for metal toxicity need to be selected carefully with respect to species, diet, age, and sex. Rats, for example, sequester some metals in their red blood cells; laboratory diets

frequently fail to reflect human diets; early development and senescence are periods of enhanced sensitivity to toxic challenges; and, sex differences in response to both deficiencies and excesses are universally acknowledged."

- The last paragraph (lines 28-31) of the section should be deleted. The statements in the paragraph concerning models and toxicity testing for assessing metals are not true, nor do they add any value to the section.

Framework Section 3.1.3.4 - Metals Mixtures.

- The SAB suggests that the opening paragraph of this section mention the importance of metals-organic mixtures. Also, the sentence in this section containing a statement about selenium being protective against arsenic with reference to Section 4.3.6 for further discussion should be deleted. This is not a good example. While selenium is an antagonist for arsenic and has been shown to inhibit arsenic's carcinogenic effects (particularly in animals), humans in developed nations have a sufficient amount of selenium in their diet and additional selenium could be toxic. In developing nations such as Bangladesh, humans may have selenium deficiency and could benefit from additional selenium in the diet. In addition, the SAB suggests the following changes to the recommendations in this section (pages 3-8 to 3-9)

  - Recommendation 1 (page 3-9, lines 9-11) in this section should be revised to include the National Academy of Sciences/National Research Council (NAS/NRC) 1988 report on the toxicity of mixtures as a reference (National Research Council, 1988). Recommendation 1 should be replaced with the following rephrasing:

    "Metal mixtures interactions and toxicity need to be clearly demonstrated by the use of: a) proper experimental design (National Research Council, 1988), b) appropriate plotting of diagrams, and c) rigorous statistical evaluation to demonstrate synergism, additivity, sub-additivity, potentiation and antagonism."

  - The SAB finds Recommendation 2 (page 3-9, line 13) in this section to be acceptable.

  - Recommendation 3 (page 3-9, line 13) in this section should be revised to include the need for identifying synergy, additivity, potentiation or antagonism using appropriate statistical analysis.

  - Recommendation 4 (page 3-9, line 22) in this section should be revised to read as follows: "There are established interactions that are based on molecular mimicry as a mechanism of action for metals. Future research goals should determine how considerations of metal mimicry may affect risk assessments and metal toxicity."

Framework Section 3.1.3.5 - Sensitive Subpopulations and Life Stages.

- The SAB finds that the recommendation in this section should be revised to read as follows: "Assessors should consider subpopulations with differing sensitivities that may

arise as a result of differential exposure (e.g., children ingest dirt) or susceptibility (e.g., elderly, immune compromised individuals, malnourishment, gender, ethnicity, genetic polymorphisms, etc)."

Framework Section 3.2.1 - Fate and Transport.

- The SAB notes that Recommendation 1 (page 3-11, line 7) in this section is a statement and not a recommendation. Recommendation 1 as currently written should therefore be inserted as part of the supporting text.

- Recommendation 2 (page 3-11, line 14) in this section is discussed in Section 4 of the Framework (Section 4.1.6.3.1 and Section 4.4.1.1.1). However, the treatment of this Recommendation in Section 4 does not provide enough detail to support the recommendation. The SAB finds, however, that Recommendation 2 in Section 3.2.1 is appropriate.

- The details of Recommendation 3 (page 3-11, line 19) in this section are discussed in Sections 4.4.1.2 and 4.4.1.1.1 of the Framework. Recommendation 3 may be an important recommendation, but it is not clearly articulated from the accompanying support material. In addition, the recommendation is very long (almost longer than the supporting text). Recommendation 3 should be shortened and supporting comments should be put back into the main text. The SAB also notes that a linkage in these models with carbon cycling is potentially important in understanding the cycling and ultimate effects of metals.

- Recommendation 4 (page 3-11, line 34) in this section addresses the use of chemical equilibrium models such as MINTEQ. The utility of computer based chemical speciation models like MINTEQ for characterizing forms of metals is given in section (4.1.4.1.2 and 4.1.6.4.1). The SAB finds that adequate support is provided for this recommendation.

- Recommendation 5 (page 3-11, line 38) in this section is discussed in Section 4 of the Framework, starting on page 4-99, and is consistent with EPA policy. The SAB notes, however, that Recommendation 5 is not written as a recommendation, but rather as a statement. Recommendation 5 should be shortened and re-stated in the form of a recommendation.

- The SAB finds that Recommendation 6 (page 3-12, line 6) in Section 3.2.1 of the Framework is well supported by text provided in the environmental chemistry section of the document. This recommendation is supported in the discussion of the limitations of solution speciation computer based models (Section 4.1.6.4.2). This issue is also given some support in the discussion on the limitation of the equilibrium partition approach in the discussion of limitations (Section 4.4.1.1.2) of the aquatic transport models. This limitation is certainly one of the most important for modeling.

- Recommendation 7 (page 3-12, line 12) of this section is supported, but not in the section of the Framework that is referenced. Rather, the limitation of the equilibrium partition

coefficient and equilibrium approach is given in the discussion of limitations of the aquatic transport models. This discussion is provided in Section 4.4.1.1.2 but not in Section 4.1.4. However, the equilibrium assumption for modeling metal partitioning to and from aged soils is a limitation that is not mentioned in Recommendation 7. The SAB notes that metals are not likely to be in readily reversible associations with solid phases in aged soils. This point on aging is made in Section 4.1.6.3. Recommendation 7 should not stand alone as a recommendation, but rather be included in the supporting text. The SAB notes that Recommendation 6 in Section 3.2.1 can encompass the issue of partition coefficients. The SAB also notes that there should be less emphasis given to static "partition coefficients" and more emphasis on dynamic partitioning processes.

- Support for Recommendation 8 (page 3-12, line 22) of this section is provided throughout the document in the discussion of the importance of oxidation state changes for certain metalloids, and in the environmental chemistry section (Section 4.1). For example, the environmental chemistry section on the importance of pH and redox conditions (Section 4.1.3.2), and the atmospheric behavior/chemistry section (Section 4.1.7) address Recommendation 8. However, it may be inappropriate to change input parameters to overcome the shortcomings of the process modeled. As such, the SAB suggests removing this recommendation and the text on page 4-101 (lines 25-33) from which it was taken.

Framework Section 3.2.2 – Water Column Exposure, Bioavailability and Effects

- The SAB finds that the recommendations contained in this section were generally well-stated and well-supported in Section 4.

Framework Section 3.2.3 - Background.

- The SAB finds that the recommendations in Section 3.2.3 (background) are generally supported by the text in Sections 4.5.4.1-4.5.4.2 of the Framework, but statements in Section 3.2.3 are not really "justified" by data (i.e., graphs showing variability). This type of "support" is probably not absolutely necessary, but in a strict sense, the Framework fails to justify the conclusion in Section 3.2.3 with data.

- The recommendation addressing the importance of considering background concentrations in metals risk assessment is discussed in various places throughout the document. It is identified as a key metal issue in the problem formulation and metals principles section (Section 2) and given specific emphasis in the human exposure pathway analysis section (Section 4.2.2.1). Background concentration effects are also discussed in the section on characterization of ecological effects (Section 4.5.4). The SAB notes that in all the recommendation statements provided in the Framework, it would be useful to indicate where the information is discussed in Section 4.

- Background metal concentrations issues are not discussed in the environmental chemistry section (Section 4.1) of the Framework. The SAB notes that in the environmental chemistry part of the document it would be useful to include a section on the natural

occurrence of metals. It would be useful to highlight in the environmental chemistry section those metals and regions for which background concentrations would be important. The issue of aging as discussed in Section 4.1.6.3 is suggestive of the relative importance of background versus recent metal inputs into soils and sediments and its implied significance to bioavailability and mobility. Similarly, a discussion of the effect of early diagenetic reactions on the fate and effects of metals would be helpful.

- The SAB finds that the relationship between the recommendations in Section 3.2.4 on bioaccumulation and the support in Section 4.5.8 is muddled by the lack of a clear presentation and consistent use of definition of "bioaccumulation factor" and "bioconcentration factor" (BAF/BCF). Once BAF/BCF are clearly defined and used consistently, it will be possible to assess these sections critically.

Framework Section 3.2.4 – Bioaccumulation.

The SAB finds that the recommendations in this section are unclear, contradictory, inconsistent, and ill supported. As discussed in the responses to charge questions 3.11, 3.12, and 3.13 below, Section 4 of the Framework does not adequately reflect the recommendations in Section 3.2.4 concerning bioaccumulation. In general, the SAB feels the EPA needs to revise the recommendations in this section to increase clarity and conciseness. For example, EPA should consider: 1) combining and reconciling Recommendations 1 and 3 (page 3-17, lines 16 and 27) in this section; 2) Combining and clarifying Recommendations 4, 5, (page 3-17 lines 31 and) and 8 (page 3-18, line 12) in this section; and 3) Combining Recommendations 6 and 7 (page 3-18, lines 1 and 5) in this section. The issue of diet must be reflected as a route of exposure in the revision. The SAB finds that Recommendation 9 (page 3-18, line 16) in this section can stand as drafted.

Framework Section 3.2.5 – Trophic Transfer, Biomagnification, and Dietary Toxicity.

- The SAB finds that Recommendation 1 (page 3-19, line 9) in this section of the Framework needs to reflect the importance of trophic transfer. It is suggested that the statement be revised by adding the phrase: "...classifying hazards or risks of inorganic metal compounds, [whereas, trophic transfer should be considered]." The SAB finds that Recommendation 2 (page 3-19, line 17) in this section should be revised to be more directed and concise. As written, the recommendation is contained in the 1st sentence. The remainder of the text is clarifying information and should be moved into the supporting text description.

Framework Section 3.2.6 – Sediment Exposure and Effects.

- The SAB finds that all of the recommendations in this section of the Framework should be reconsidered in light of the discussion contained in the response to charge question 3.14 below.

Framework Section 3.2.7 – Metals Mixtures.

- The SAB finds that the discussion in Chapter 4 that is related to the recommendations in Section 3.2.7 of the Framework should be further developed. EPA should consider the addition of a recommendation to address the inclusion of empirical studies of metals mixtures in the field. The SAB finds that the "field" part is left out of the current version of the Framework. Finally, the SAB finds that the concept of Quantitative Ion Activity Relationships (QICAR) is not well developed in Sections 3 or 4. EPA needs to justify that this concept is sufficiently well developed and validated to be included in such a specific recommendation.

Framework Section 3.3.1.1 - Atmospheric Chemistry and Behavior.

- The SAB finds that Recommendation 1 (page 3-22, line 18) in this section is not a recommendation. It should therefore be removed and included as commentary in the paragraph description. The SAB also notes that the Community Multi-Scale Air Quality (CMAC) Model is not mentioned by name in Section 4.1.7 as implied by the referencing to Section 4.1.7.

Framework Section 3.3.1.2 – Soil Mobility.

- The SAB finds that Recommendation 1 (page 3-23, line 6) in this section is simply a list of measurement techniques and not necessarily a recommendation. Little supporting information is given on the utility of each technique and how the information may be useful in a risk analysis context. Some chemical techniques and speciation tools are covered in the referenced environmental chemistry section (Section 4.1.8). However, if the point to be made in this section of the Framework is that these tools should be used to help with site specific assessment of metals, and to provide guidance on relative mobility, then this should be stated in Recommendation 1. The SAB also notes that little information is provided in the Framework about analytical chemical methods that are currently commonly used for metal ion speciation.

- The SAB finds that Recommendation 2 (page 3-23, line 15) in this section is not a recommendation but a statement. Supporting information on the need to use computer models for predicting speciation changes in soil solutions is provided in the environmental chemistry section (Section 4.1.6.4.1.1.). The SAB suggests that an appropriate statement to be included in Recommendation 2 would be that computer speciation models should be considered when: 1) a more definitive analysis of the impact of metal ion speciation in metal risk assessment is required for site specific level risk characterization, 2) the model assumptions are appropriate for the application, and 3) sufficient site characterization data are available.

- The SAB finds that Recommendation 3 (page 3-23, line 20) in this section is well supported in the Framework. However the recommendation is not stated in the form of a recommendation. The SAB suggests that Recommendation 3 might be restated to emphasize that K_d values can only be used when they are either calibrated for a specific

site, or have sufficient functionality built in to account for the variability of K_d with important changes in solution conditions such as pH and soil composition effects. Discussion of K_d is provided in the environmental chemistry section of the Framework (Section 4.1.4.1.3) and the section of the Framework addressing the limitations of using K_d (Section 4.1.4.1.4).

- The SAB finds that Recommendation 4 (page 3-23, line 26) in this section is not a recommendation. Supporting information about the MINTEQ model is provided in the environmental chemistry section on metal sorption modeling (Section 4.1.4.1.2). In Sections 4.1.4.1.2 and 4.1.4.1.5 of the Framework it is indicated that the Diffuse Layer Surface Complexation Model (DL Model) can be used to generate generic partition coefficients, and that one can use the DL sorption model for screening level assessment of metal ion mobility and in the site specific definitive assessment of sorption and mobility. However, the SAB notes that as the recommendations are not meant to be prescriptive, the Framework should mention other applicable models with the same capabilities as MINTEQ, such as MINEQL+ and PHREEQC.

- The SAB finds that Recommendation 5 (page 3-23, line 30) of this section is not a recommendation but rather a statement. Support for this statement with respect to metal cations is provided in the environmental chemistry section (Section 4.1.4.1.3.), but support for the statement is not provided with respect to oxyanions. The applicability of a varying pH K_d value for anion sorption should be added to the chemistry section, although the motivation for an inverse dependency of anion sorption with increasing pH is given in Section 4.1.6.2.2.

- The SAB finds that Recommendation 6 (page 3-23, line 38) in this section concerning estimation of metal adsorption is not a recommendation but a statement. Support for this statement is provided in the environmental chemistry section (Section 4.1.4.1.3.) but this support is not backed up with reference to literature reporting where this approach has been previously used successfully. Recommendation 6 is a condensed version of two statements that are given without supporting information in the environmental chemistry section. For example, the Framework does not indicate in the section of the document addressing models that it would be difficult in practice to estimate the amounts and surface areas for composite soil and sediment materials. The SAB also notes that a statement should be included in the Framework to indicate that, in addition to obtaining relevant sorption parameters, quantifying the amount for the major sorbing fractions is one of the major challenges for applying surface complexation sorption models. In practice, this would probably be a fitting parameter in the way models might be applied for screening or site-specific assessments. It is not clear whether or not this should stand alone as a recommendation or be a part of the discussion in the supporting text.

- The SAB finds that Recommendation 7 (page 3-24, line 2) in this section is not a recommendation but a statement. Discussion of this statement is provided in the environmental chemistry section (Section 4.1.4.1.5). In view of the discussion of the potential shortcomings of using single or averaged literature Kd values or generic forms that depend on soil properties, Recommendation 7 is amply supported by the information

provided in the environmental chemistry section. As stated previously, one must also account for changing environmental conditions.

- The SAB finds that Recommendation 7 (page 3-24, line 5) in this section is not a recommendation. Discussion of the Generalized Two-Layer Model (GTLM) is provided in Section 4.1.4.1.2 of the Framework. However, support for the requirement of isotropic fluid flow and fast, reversible, and linear sorption is not given in the environmental chemistry section of the Framework. The inherent assumption of isotropic fluid flow, however, is common to transport models. While the need for fast and reversible sorption is true, linear sorption is not required per se. One of the attributes of the GTLM is that it can account for the nonlinearities in sorption as a function of pH and changing amounts of solid to liquid. The SAB notes that little discussion was provided in the Framework on the conditions under which the use of models is appropriate. The SAB suggests that a more elaborate discussion of the limitations (data or field conditions) be added to the metal sorption section to describe the types of scenarios where such models are appropriate. In general, the SAB finds that the discussion in the Framework of sub-surface transport is limited.

- Recommendation 7 (page 3-24, line 10) in this section of the Framework addresses the PHREEQC model. It is not clear why a separate recommendation is needed concerning PHREEQC unless the point to be made is that three dimensional models are also now available that couple metal ion surface complexation models with transport. The SAB finds that Recommendation 7 is largely a repeat of the same sentence from Section 4.1.4.1.2 of the Framework. The sentence is given there without further discussion.

Framework Section 3.3.2.2 – Soil Invertebrates and Plants.

- The SAB finds that the recommendations in this section of the Framework should be revisited and revised in light of comments in the response to charge question 3.11 below.

Framework Section 3.3.2.2.1 – Soil Invertebrates.

- The SAB finds that the recommendations in this section of the Framework are well-stated and well-supported.

Framework Section 3.3.2.2.2 – Plants.

- The SAB finds that the recommendations in this section of the Framework (as drafted) should be reduced in scope such that the actual recommendations are clearly stated and the explanatory statements are moved to the supporting text. The text in Recommendation 1 (page 3-28, line 33) in this section, reflecting the soil plant barrier concept, needs to be shortened but expanded in supporting paragraphs. Recommendation 3 (page 3-29, line 12) in this section, discussing the issue of aerial deposition, should be reconsidered and dropped or revised to reflect supporting information. The SAB finds that this recommendation is not adequately supported by text. The SAB finds that Recommendation 4 (page 3-29, line 16) in this section is a statement not a

recommendation and should be moved to the supporting text.

Framework Section 3.3.2.3 – Wildlife.

- The SAB finds that the recommendations in this section of the Framework are well defined and adequately supported. It is suggested that Recommendation 5 in this section be revised as follows: "Although bioaccumulation and trophic transfer of metals does occur [and should be considered], with some exceptions (e.g., selenium and mercury) biomagnification (i.e., increases in concentration through the food web) is a less important consideration and may be assumed to be unimportant." Recommendations 3, 4, and 5 in this section should be combined into a single recommendation. Recommendation 5 in this section contains a reference to the general scientific literature. This should be relocated to another part of the document.

Framework Section 3.3.2.4 – Food Chain Modeling.

- The SAB finds that the recommendations in this section should be revised to make them more concise. Recommendation 2 (page 3-31, line 9) in this section of the Framework is not a recommendation and should be moved to the supporting text. Recommendations 3, 4, and 5 (page 3-31, lines 11, 25, and 29) of this section should be consolidated into a single recommendation.

Framework Section 3.3.2.5 – Bioaccumulation.

- EPA should reconsider and re-evaluate the recommendations in this section in the light of previous comments, and make sure that parallels between soils and sediments are developed.

Framework Section 3.3.3.1 – Adaptation and Acclimation.

- The SAB finds that there is confusion about what is intended in the Framework by the term "acclimation." It is unclear whether EPA is addressing the question of "true" metals acclimation and the resulting increase in tolerance and/or resistance, or suggesting that care should be taken in culturing organisms for testing to ensure that they are not "overly sensitive" owing to the fact that they were raised in metals-deficient conditions.

Framework Section 3.3.3.2 – Essentiality.

- The SAB finds that Recommendations 1 (page 3-35, line 23) and 5 (page 3-36, line 2) in this section be removed and incorporated into the supporting text of the document because they are not recommendations, but rather informational statements.

Framework Section 3.3.3.3 – Metals Mixtures.

- In general, the SAB finds that the metals mixtures recommendations in this section of the Framework are adequate. However, the SAB notes that there is a need to be mindful of

the importance of evaluations conducted in the “real world.”

Framework Section 3.3.3.4 – Toxicity Testing.

- The SAB finds that the recommendations for toxicity testing and extrapolation of effects, as developed for terrestrial ecosystems, need to be developed and included in the aquatic section of the Framework. Toxicity testing of metals has strengths and limits as an assessment tool metals. For example, limits derive from: the use of surrogate species versus the diversity of responses to metals, among metals and among species; and the lack of dietary exposures in the toxicity testing data bases usually used by risk assessors. There are unique effects of metals that are well known in some aquatic environments (e.g., stream insect communities; selenium and mercury effects on upper trophic levels) and poorly known in others. In light of these considerations, the SAB finds that the recommendations in this section are not well articulated with regard to evaluation of national and site specific risk from metals. The recommendations contained in this section need to be concise and explanatory text needs to be moved into the supporting body of text. The SAB finds that the recommendations in the section were generally supported by the text in Section 4 of the Framework.

Framework Section 3.3.3.5 – Extrapolation of Effects.

- The SAB finds that actual recommendations need to be made and “statements” moved into the text. For example, Recommendation 4 in this section is a statement. The SAB finds that the recommendations in this section are not well-supported by information in Section 4 of the Framework.

Additional, Specific Comments on Section 3 of the Framework

The SAB provides the following additional specific comments on the metals risk assessment recommendations section of the Framework document. The pertinent pages and line numbers in Section 3 of the Framework are referenced below.

- Some of the recommendations in Section 3 of the Framework are not sufficiently specific to be useful. On page 3-11, for example, the following recommendation is made about use of chemical equilibrium models: "Most of the available transport models do not currently include chemical speciation subroutines. In such cases, chemical equilibrium models such as MINTEQ serve as useful alternatives for characterizing the forms of metal that are present." This statement is not incorrect, but it is not clear how chemical equilibrium models can be used to consider speciation in transport assessments.

- Page 3-10, lines 31-32: In light of discussions in Section 4 of the Framework and in the issue paper on the environmental chemistry of metals, it would be more appropriate to state that partitioning (and not partition coefficients) are important. This statement should be followed by a discussion of how chemical speciation calculations are preferred in determining metal partitioning, but in situations where sufficient data and modeling tools are not available, partition coefficients should be assigned with great care to account

for the effects of pH, inorganic and organic ligand concentrations, competitive interactions, and redox chemistry. Although the comments on partitioning and partition coefficients may seem minor, it is important that the EPA begin to move away from the paradigm of partition coefficients for metals and place greater emphasis on the more appropriate concept of metal speciation. The attention of risk assessors should be drawn more directly to the use of the MINTEQ model to relate metal speciation to soil-water or particle-water partition coefficients, such as one would use in a transport model. In addition, risk assessors must be advised to carefully investigate the effects of changes in key environmental parameters, such as pH, DOC, and particle composition on metal speciation and partition coefficients, whether they are calculated using MINTEQ or obtained by measurement. In this way, a commonly available tool, MINTEQ, can serve as both a conceptual and practical bridge between the more rigorous concepts and approaches implied by "metal speciation" and the more familiar concepts and empiricism of the "partition coefficient."

- Page 3-11, line 24: In complex models, organic carbon cycling should specifically be included to account for temporal and spatial changes in particulate organic carbon (POC), dissolved organic carbon (DOC), redox conditions, and for Hg assessments, sulfate reduction rates. It is therefore recommended that EPA add organic carbon modeling to line 24 (e.g., as "hydrodynamic, sediment transport, organic carbon cycling, and chemical transport algorithms").

- Page 3-12, line 12-20: The focus should be on metal partitioning (and not partition coefficients). In addition to the recommendation for further consideration of equilibrium assumption, it may be even more important to recommend an appropriate approach for calculating metal partitioning from chemical speciation calculations, and when sufficient data and modeling expertise is not available, to state what factors need to be considered in assigning a partition coefficient.

- Page 3-14, lines 36-37: Quantitative Ion Character Activity Relationships (QICARs) appear to be an important tool for extrapolation of metal availability and toxicity data. However, the detailed discussion of QICARs on pages 4-153 and 4-154 is very brief and could be further developed.

- Page 3-18, lines 1-3: Discussions in Section 4 of the Framework on biotic ligand models focus on bioavailability and toxicity from metal binding at the gill. The SAB notes that there are no discussions on how biotic ligand models have been used in estimating bioaccumulation.

- Page 3-19, lines 9-15: In discussing the rarity of metal bioaccumulation, a qualifying statement should be added for the methylmercury and organoselenium exceptions.

- Page 3-21, lines 22-23: It is not clear from discussions in Section 4 of the Framework that the BLM has been applied to metal mixtures.

- The recommendations in Section 3 of the Framework are often given without the

precautionary statements that were part of discussions in Section 4 of the document. For example, Section 4 indicates the limitations of several approaches when applied to clay-rich sediments and soils.

- In general, all of the "recommendations" under soil mobility (Section 3.3.1.2) need to be reworded and stated in the form of recommendations or it should be stated at the beginning of Section 3 of the Framework that the lists are guidance statements or recommendations rather than just recommendations.

- Although organo-metal transformation processes are discussed in the environmental chemistry section of the Framework (Section 4.1.9), the recommendations at the end of Section 3.3.1.3 (transformation in soils, page 3-25) are not taken directly from the information provided. Any recommendation listed in Section 3, should follow naturally from the information and context provided in Section 4. The summary paragraph in Section 3 and the recommendations listed in Section 3.3.1.3 do not seem to be taken from the Section 4 summary on organo-metal transformations.

- Page 3-10, lines 23-25: Regarding model complexity, the statement that more complex models are not necessarily better gives no basis for decision. Calibration is arguably the key issue in making this choice and discussion of this point would be helpful.

- Page 3-11: The discussion of partitioning seems out of place given critique of partitioning that is provided later in the Framework.

- Page 3-14: Hardness (competing cationic metals) is a factor that is independent from speciation. The suggestion to only use it when speciation data are not available does not make sense.

- Section 3.2.3: Default use of state averages for backgrounds would be erroneous if non-point sources are significant in comparison to geological sources. The SAB notes that this could be ascertained on a metal-by-metal basis prior to adopting state average as a background.

- Section 3.2.4: The discussion in the Framework concerning the appropriate use of BCF/BAF is confusing. Paragraphs at the bottom of page 3-16 and top of page 3-17 seem to offer conflicting statements concerning the use of BCF/BAF.

- Page 3-17, lines 8-9: The statement concerning whole body concentration and potential for toxicological impact is likely to be true, but the question of correlation between whole body concentrations and concentrations in specific organs/sites should be considered.

- Section 3.2.6: Recommendation of the use of the SEM-AVS approach without considering other approaches is neither balanced nor justified

Appendix B. Speciation

Among risk assessors and scientists working on the environmental chemistry and ecotoxicology of metals, the concept of "chemical speciation" is fundamental. Despite this fact, or perhaps because of it, a variety of context-specific uses of the term, along with the related term "chemical species," have developed. This practice can confuse newcomers to the field, perhaps even hindering their apprehension of concepts that are not in themselves difficult. To remedy this situation, the SAB recommends that the environmental chemistry section begin with a set of definitions adapted from recent IUPAC recommendations (Templeton et al., 2000). Quotations from this source are in italics.

Species: *Chemical compounds that differ in isotopic composition, conformation, oxidation or electronic state, or in the nature of their complexed or covalently bound substituents, can be regarded as distinct* ***chemical species****.*

In environmental chemistry, the phase the species occurs in - gas, liquid, aqueous solution, mineral, or adsorbed on an interface between phases - generally is also specified in a complete definition.

Note that this definition applies equally to the environmental chemistry of organic compounds and of metal ions, although there are important differences in how the term is used in practice. In the context of the environmental chemistry of metals, chemists speak of a metal species as a *"specific form of an element defined as to isotopic composition, electronic or oxidation state, complex or molecular structure"* and phase. In the context of environmental organic chemistry, chemists do not usually refer to an organic compound as specific form of carbon, although every organic compound is one. Rather, as long as its core structure remains intact, each different protonation state, complex of a metal ion, and occurrence in different phases of an organic compound may be referred to as a different *species of the compound*.

Speciation: According to the above definition of species, it is apparent that the reactants and products of any properly written chemical reaction are distinct chemical species. Indeed, the concepts of species and reactions are intimately related since any process that brings about a chemical change by definition results in the formation of a new species. As a result of this logical relationship, and possibly also its parallel to the concept of evolutionary "speciation" in biology, some geochemists and environmental chemists have *"applied the word speciation to describe the transformations taking place during cycling of the elements."* However, the IUPAC has recommended against this use of "speciation," instead suggesting the term **species transformation**. Given its consistency with the usage of "transformation" in the field of environmental organic chemistry, this recommendation should be easily accepted and put into practice.

The IUPAC also recommends against using the term ***speciation*** *to indicate the analytical activity of identifying chemical species and measuring their distribution. Sometimes, it is used to indicate that a method gives more information on the form in which the element is present than other more commonly applied techniques (e.g., measuring distinct organomercury compounds as opposed to a total mercury determination). In order to avoid confusion, [IUPAC] recommends*

*using the term **speciation analysis** when referring to the analytical activity of identifying and measuring species*.

Instead, the IUPAC-recommended use of ***speciation*** *is the distribution of an element amongst defined chemical species in a system*. Normally, a quantitative description of the speciation of an element is implied. Such a distribution could be the result of: i) one or more chemical analyses of a sample, ii) chemical modeling of a laboratory solution of known composition, or iii) chemical modeling of an environmental system. When not clear from the context, the terms *analytical speciation and modeled speciation* may be helpful in distinguishing these methods used to obtain the speciation.

As a practical matter, the degree of resolution adopted in any description of the speciation of a system will depend on:

i) *the relevance of the species differences for our understanding of the system under study,*
ii) *our ability to distinguish between the various species analytically,*
iii) *our ability to model the speciation in some operationally-defined or experimentally-controlled fraction of an analyzed substance.*

While some analytical methods directly determine the concentration of a single species in an environmental sample or matrix, most common environmental analyses measure several related species, or **fractions**. IUPAC recommends that the *process of classification of an analyte or a group of analytes from a certain sample according to physical (e.g., size, solubility) or chemical (e.g., bonding, reactivity) properties* undertaken by a chemical analyst be referred to as **fractionation**.

Appendix C. Suggested Editorial/Wording Changes

Section 2 of the Framework

- Section 2.1.7 discusses toxicity testing and implies that toxicity is the metal impact of primary concern. However, the SAB notes that metal effects on the environment can be much broader than effects measured in a toxicity test endpoint (e.g., long-term impacts on ecosystem structure). The SAB therefore suggests that the factor be re-named and discussed as "toxicity." The terrestrial part of Section 3 (Sections 3.3.3.4 and 3.3.3.5) extends "toxicity testing" to include "extrapolation to effects" (in nature). The SAB recommends that the problem definition of "toxicity" in Section 2 be clarified in a similar way. It is important to take into account limits and linkages between toxicity testing and adverse effects. Both Section 4 and EPA's Metals Issue Papers include useful discussions of effects of metals on populations and communities of organisms.

- The linkage of Figure 2-3 to the text could be enhanced by modifying the footnote box "Key Metal Issues" in Figure 2-3 to include references to specific subsections in the text. The footnote box should be reconsidered to determine how well it clarifies the figure and relates the figure's components to the text. The SAB suggests that the footnotes to Figure 2-3 might be improved by listing just the key factors that impact the conceptual model components shown. The SAB offers the following specific comments on Figure 2-3.

  - The footnotes to Figure 2-3 would be easier to understand if the words were not abbreviated in the description of M1 through M9 in the figure legend.

  - The footnote referring to M1 of Figure 2-3 should include organic carbon cycling.

  - The meaning of "concentration dependency" in the footnote referring to M2 of Figure 2-3 is unclear.

  - In the blocks on Figure 2-3, the word "chemical" should be changed to "metal".

- The conceptual model represented in Figure 2-3 was developed to describe the assessment of classes of metals identified in Table 2-1 in Section 2 in the Framework. The SAB offers the following specific comments on the lists of metals in Table 2-1:

  - Mg is an essential metal and should be added to Table 2-1.

  - Silicon is in Table 2-4 but not in Table 1-2 of Section 1. For consistency, these tables should have the same elements.

  - It is unclear why the particular metals in Tables 1-2 and 2-1 were selected to be included in the tables, and why others were omitted. Some comment should be included concerning risk assessment for other metals such as tungsten, uranium, or tellurium that may be important in local, regional, or national settings. This is

discussed in lines 9 to 13 of page 1-3 in the Framework, but the relevance to all metals should be repeated in introducing Table 2-1.

- The SAB suggests that the Framework contain references to the work of authoritative scientific panels charged with making recommendations regarding essential metals, such as the National Academy of Sciences (2000). If changes occur in this field over time, readers can be directed to these more up-to-date sources of information. The SAB also notes that the following reviews by individual experts on chromium essentiality should be cited: Hathcock (1996), Lukaski (1999), Mertz (1993), Mertz (1995), and Wallach (1985). Additional comments on the list of metals included in Table 2-1, and the classifications presented there, are provided in the response to Charge Question 3.9.

Sections 3 and 4 of the Framework

- The concept of soils and the terminology associated with soil substrates needs to be clearly defined and the text should be revised to accommodate modern nomenclature in soil science for organic and mineral soil horizons and soil types. Concepts used should accommodate soil substrates in urban, wetland, forested, agronomic and disturbed ecosystem contexts consistent with U.S. Department of Agriculture (USDA) Natural Resource Conservation Service (NRCS) terminology. Several soil properties (e.g., pH, cation exchange capacity [CEC]) are often discussed in this Section 3.3 of the Framework because of their appropriate importance in metal risk assessment activities. These properties can be highly operationally defined based on the methods chosen but there is only a passing mention in the Framework of the importance of methods. This subject should be explicitly developed.

- A statement should be included about the potential for longer-scale transport of metals from a source through the atmosphere to soil, water, or air, from which exposure ultimately occurs. Even if the process for metals follows principles already established and described for organic compounds, and EPA does not want to repeat that description in the Framework, a statement about the similarities and differences between inorganic and organic compounds would improve the completeness of the Framework. For example, while many metals are transported in the atmosphere primarily only on the surfaces of particles, many organic compounds are transported in the atmosphere primarily as a component of the vapor phase.

- A statement about the potential importance of atmospheric transport to “background” concentrations of metals in the environment should be included either in the section of the Framework discussing atmospheric chemistry or in the “background” section.

- The SAB notes that, EPA has used the term, “duff”, in the terrestrial section of the Framework (page 3-27) when discussing factors influencing metal availability and accumulation. This term is many decades out of date. The SAB therefore suggests that EPA delete the term and instead use the “O horizon or litter layer.” Use of the correct terminology is important in order to address concerns about soil measurements and soil

concepts. In a forest region, the forest floor horizon is the O horizon. Standardizing soil to the top 10 – 12 cm is not appropriate across a range of ecosystem conditions to include urban, wetland, undisturbed forest, agronomic, and disturbed systems. A more appropriate nomenclature for soil horizons and types consistent with USDA NRCS terminology should be defined and used.

The SAB notes that the following statements in Section 4 should be checked for accuracy and, as warranted, corrected:

- Page 4.3, line 1: The order of the metal sulfides appears to be incorrect. Iron should be moved between zinc and manganese. The solubility constants cited should be checked against established compilations of thermodynamic data.

- Page 4-40: The equation showing dimethylmercury photolysis should be checked. Dimethylmercury does not absorb sunlight directly and direct photolysis is unlikely. Formation of two methyl radicals is also unlikely. Atmospheric oxidants, however, would be expected to oxidize dimethylmercury (as discussed in the last paragraph on the page). Also, demethylation is unlikely to occur via sorption to particulate matter, as suggested in line 31 of the same page.

- Page 4-42, lines 15-16: The statement that 15-30 percent of arsenic is volatilized is almost certainly due to arsine (AsH_3), rather than methylation. Thus, the statement is out of place in a methylation paragraph.

- Page 4-40: The atmospheric transformation sections appear to be written in a manner that is inconsistent with other sections (e.g., paragraph length and formatting). The sections are very short, relative to the previous or following sections.

- Page 4-39, line 7: The following text should be reworded ". . . formation of less bioavailably charged metal-sulfur complexes". The SAB questions whether the metal sulfur complexes are actually charged.

- Page 4-39, line 11: Use of the word "unbioavailable" appears to be a bit awkward.

The following specific revisions are also suggested by the SAB to improve the clarity of Section 4.2.1.

- Page 4-2, lines 8-10: The introductory paragraph contains broad generalities that are not all strictly accurate; it should be completely rewritten. EPA should define "acids" and "bases" and then state which metal species are usually acids and which ligand atoms are usually bases.

- Page 4-2, lines 12-13 and 15: Revise the document to qualify and/or provide references for the statement about "toxic reaction" being directly related to the nature of the metal at the surface of the organism, and the statement about toxicity. This is addressed in the comment above on toxicity.

- Page 4-2, line 16: Change “introduced” to “described” because the concept was introduced earlier by Pearson (1963) and others (Arhland et al., 1958; Schwarzenbach, 1956) in the 1950’s.

- Page 4-2, line 17: Delete “in this concept” because the statement is true in general.

- Page 4-2, line 21: Delete “mobile and easily moved” to avoid confusion with oxidation-reduction reactions; “deformable” and “polarizable” are the appropriate terms.

- Page 4-2: If a box is necessary to define “ligand,” a box should also be used to define “complex.”

- Page 4-3, line 1: Delete the clause “which are less toxic;” such statements about relative toxicity can be included in the text, where appropriate justification and qualification can be given, rather than in the title where it appears without justification and qualification.

- Page 4-3, line 2: The U.S. spelling of sulfur should be used.

- Page 4-3, lines 2-3: The appropriate term to be used is “extent of binding,” not “strength of binding” because the strength is intrinsic to the metal and ligand, and the pH effect is more accurately described as a competition effect.

- Page 4-3, line 5: Change “many of the hard metals” to “some of the hard acids;” to avoid confusion, use the terminology “hard and soft acid” consistently, don’t switch to “hard and soft metals.”