Framework for Metals Risk Assessment
EPA Response to Peer Review Comments
February 28, 2007

EPA's Science Advisory Board (SAB) conducted the external peer review of the *Framework for Metals Risk Assessment* in February 2005. The SAB report (available at http://www.epa.gov/sab/pdf/metals_sab-06-002.pdf) notes that the *Framework* covers the main areas of concern to risk assessors. The SAB observed, however, that the draft *Framework* also included information more appropriate to a handbook of methods. Therefore, the SAB suggested that the document be restructured and revised to improve the clarity and precision of its discussions, in addition to some technical corrections and additions. Below is a compilation of EPA's responses to the SAB recommendations. Specifically, EPA chose to revise the document so that its focus was that of a framework. Thus, the issues raised with regard to models and methods are left to be addressed in documents on those topics. The final draft of the *Framework for Metals Risk Assessment* was completed January 25, 2006.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
SAB Cover Letter (January 25, 2006) 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 Framework has been reorganized and shortened to focus on the Principles for risk assessment of metals and how they apply to human health, aquatic, and terrestrial risk assessments. The Principles have been developed beyond a simple list of factors to be considered. The Conceptual Model is used to illustrate key concepts and to clarify the distinctions among different types of chemicals and applications of risk assessment. The revised Framework provides the rationale for excluding organometallic compounds from the document. It does include discussions of natural transformation pathways that form organometallic compounds. The revised Framework does not include guidance on tools and methods. Where tools and methods are introduced, they serve as examples illustrating the Principles of the Framework. The Principles are also highlighted through sets of assessment questions that risk assessors should consider for human health or ecological applications. Because the revised Framework is not intended as a technical guidance document, it does not provide in-depth discussions of the strengths and limitations of tools and it does not provide recommendations on the use of specific tools. This type of guidance will be presented in future documents that complement and expand upon the Framework. The revised Framework provides more balance in the discussion of human health and ecological assessments. Important terms such as bioaccumulation and speciation are now clearly defined and where appropriate a common set of terms is used for both human health and ecological assessments of metals. The title has been revised to the Framework for Metals Risk Assessment.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
SAB Cover Letter (January 25, 2006) 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 Human Health section has been completely revised and SAB specific comments addressed as described in detail later in these response to comments.
SAB Cover Letter (January 25, 2006) 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 revised Framework addresses an overarching comment from the SAB concerning its purpose. The Framework is not a technical guidance document and therefore does not provide a critical evaluation of tools and methods.
SAB Cover Letter (January 25, 2006) The Recommendations Section of the Framework should be revised to reduce the overall number of recommendations by combining redundancies and eliminating those statements that are not recommendations. Recommendations in the Framework should also be organized according to their specificity (i.e., from general overarching to more specific), and each recommendation should be adequately supported by text and references as appropriate.	The revised Framework includes a short recommendations section. This section no longer deals with specific tools and methods but addresses the applications of Principles.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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."	As noted earlier, the revised Framework focuses on Principles and how these are applied. Guidance on the use of methods or tools has been removed except as used as illustrative examples. This material will be used in technical guidance documents at a later date.
1. Executive Summary *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.	Please see previous responses. The scales of assessment are introduced in Section 2 of the revised Framework and now discussed more explicitly for human health, aquatic, and terrestrial assessments (Sections 4 – 6).

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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.	A set of Principles has been developed that amplify the "Factors" described by the SAB. Assessment Questions are used to highlight the Principles for human health, aquatic, and terrestrial assessments.
1. Executive Summary *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.	The conceptual model has been revised to emphasize the key concepts. The conceptual model now forms a key part of the new Section 2 which provides a foundation for the Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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.	The revised Framework provides recommendations that pertain only to the application of the Principles. Although methods and tools are introduced to illustrate the applications of Principles, no recommendations are provided on using specific tools or on their strengths and limitations. This is consistent with the Framework serving as an overarching document rather than technical guidance.
1. Executive Summary *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.	Particulate matter: The revised Framework now includes a more complete discussion of particulate matter at a level appropriate for the Framework. Particulate matter less than 2.5 microns in size is of particular concern for human health risk assessment, due to the ability of these particles to penetrate deeply into the lung. The EPA methodology for addressing such particulate matter is addressed, as noted in the next bullet. However, the human health implications of exposure to nanoparticles is still a developing science area. The developing literature suggests that current dosimetry models and traditional dose measures (such as concentration in mass/unit volume) may not adequately characterize human health risk to micro metal particles. The document highlights assessment questions to inform the risk assessor, and notes that the field of nanoparticle risk assessment is developing. These points are addressed in Section 4.2.5.1.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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: 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.	Inhaled particles: The revised Framework now includes a more complete discussion regarding this exposure pathway at a level appropriate for the Framework. Characteristics of inhaled particles and implications for risk assessment have been addressed in Section 4.2.5.1. U.S. EPA has existing guidance on inhalation dosimetry methods for human health risk assessment. The existing methodology includes consideration of key factors related to metals, including particle size and shape characteristics, solubility considerations, and physiology related to assessing deposited dose in humans and several common laboratory animal species. The current EPA guidance is under revision and additional new dosimetry models (e.g., the multipathway particle dosimetry model) have been developed that allow for improved lung dose estimations due to additional consideration of life-stage specific parameters, respiratory tract clearance, and differences in oronasal breathing patterns with work load. Key assessment questions and current U.S. EPA guidance related to inhalation dosimetry for particles are discussed.

1. Executive Summary *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: 3. Inhaled mixtures. Biological effects of inhaled mixtures such as metals in combination with other airborne pollutants are not addressed in the Framework.	Mixtures: The revised Framework now includes a more complete discussion of mixtures at a level appropriate for the Framework. The implications of exposures to mixtures are addressed in Sections 1.4.2, 4.3.1, 5.3.3, and 6.3.3. Evaluation of data on metals requires consideration of mixtures, either of various forms of the same metal (valence state or chemical form) or combinations of metals with other pollutants. Interactions between metals are of particular importance and are highlighted in Section 2. The revised Framework also highlights assessment questions and issues associated with: 1) techniques and guidance are available for evaluating the contribution of a specific metal (or metal species) of interest, given exposure to a matrix of materials; 2) developed guidance for assessing the toxicity of chemical mixtures.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

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1. Executive Summary *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: 4. Dermal exposure and uptake of metals. Dermal exposure and uptake of metals are not adequately addressed in the Framework.	Dermal exposure: The revised Framework now includes a more complete discussion of dermal exposure at a level appropriate for the Framework. Exposure considerations related to dermal exposure are presented in Section 4.2.5.5, while toxicokinetic considerations are presented in Section 4.3.4. Full consideration of the human health implications of dermal contact with metals is complex, with a number of issues needing consideration. Key assessment questions related to the complex implications of dermal exposure are provided in the revised Framework.

1. Executive Summary *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: 5. Effects of metals at low doses. The Framework does not provide a discussion of the toxic effects of metals at low doses.	Effects of Metals at low doses: The revised Framework now includes a more complete discussion of effects of metals at low doses at a level appropriate for the Framework. Considerations related to dose-response, and the health impacts of deficiency of essential elements are addressed in Section 4.3.6 and 5.3.1, respectively. However, since individual metals are addressed primarily in the context of highlighting broader concepts, the specifics of the shape of the dose-response curve for individual metals were not addressed, and are beyond the scope of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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: 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.	Interactions between metals and organics: The revised Framework now includes a discussion of these types of interactions at a level appropriate for the Framework. This topic is discussed in Section 4.3.4 as part of the broader discussion of interactions and mixtures and includes examples.
1. Executive Summary *Objectivity and Utility of the Data, Tools, and Methods in Section 4 of the Framework (Charge question 3.2)* 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.	As noted in previous responses, the revised Framework is not intended to provide in-depth reviews or recommendations on tools and methods.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Objectivity and Utility of the Data, Tools, and Methods in Section 4 of the Framework (Charge question 3.2)* 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 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.	Bioaccumulation and bioavailability: The use of bioaccumulation as a way to assess bioavailability in aquatic systems is presented in Section 5.2 of the revised section on aquatic assessments. Toxicity testing uncertainties: Section 5.3 discusses how toxicity tests may not capture important processes that occur in situ. Controversies surrounding SEM-AVS approach: in keeping with the purpose of the revised Framework, a detailed evaluation and assessment of strengths and weaknesses of particular approaches are not included. Section 5.2.5.2 notes that controversy exists about generalizations from the SEM-AVS approach. Limits of the biotic ligand model (BLM) approach: The revised Framework does not include a detailed evaluation and assessment of strengths and weaknesses of particular approaches. Section 5.2.5.1 notes that the BLM is only applicable to acute toxicity.

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SAB Recommendation	Action Taken
1. Executive Summary *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.	This has been addressed in the new Chemistry sub-section (3.1) and in sections specific to human health and ecological risk assessment. Executive summary comments are for the most part duplications of comments in body of document. See responses regarding specific sections below.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *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.	The revised Framework includes a short section on recommendations and this material was revised. To the extent that material can be summarized in tables, efforts have been made to simplify presentation.
1. Executive Summary *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.	The discussion of the Hard Soft Acid Base Concept has been reduced in the revised Framework. This discussion is provided in the Environmental Chemistry section. It does not include a discussion on toxicity. Executive summary comments are for the most part duplications of comments in body of document. See responses regarding specific sections below.
1. Executive Summary *Environmental Chemistry (Charge questions 3.5 – 3.7)* • *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.	The Framework presents a broad overview of atmospheric transport and exposure. It does not attempt to provide in-depth guidance on atmospheric transport. When and if such guidance is eventually developed, specialists internal and external to the Agency will be engaged to help develop that aspect of exposure.

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SAB Recommendation	Action Taken
1. Executive Summary *Environmental Chemistry (Charge questions 3.5 – 3.7)* • *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.	The revised Framework does not attempt to be comprehensive with respect to the strengths and limitations of specific models. Instead it provides examples that highlight Principles and other considerations for risk assessment. This is viewed as a distinction between a Framework document and a technical guidance document.

1. Executive Summary *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.	Definitions of these terms were added to the glossary of the revised Framework, and text was added in Section 4.3.4 on toxicokinetics to address this issue. This added text addresses the risk assessment uses and implications of body burden.

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SAB Recommendation	Action Taken
1. Executive Summary *Human Exposures and Effects (Charge questions 3.8 – 3.10)* • *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.	Essentiality is addressed primarily in Section 1.4.3 of the revised Framework as it as part of the Principles. It is further discussed in the section devoted to human health assessments as well as in the aquatic and terrestrial sections. Section 4.3.2 of the revised Framework defines essentiality in terms of human health and differentiates between deficiency and high dose toxic effects. The consequences of deficiency and excess of essential metals are discussed. The speciation, route of exposure and interactions, including mimicry, can all play their part in the effects of deficiency or excess of essential metals. The revised organization of the framework separately addresses essentiality in humans and essentiality in other organisms.
1. Executive Summary *Human Exposures and Effects (Charge questions 3.8 – 3.10)* • *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.	The revised Framework addresses mixtures within the discussion of the Principles. Mixture-related effects are further discussed in the sections on human health, aquatic, and terrestrial assessments. For human health, the Toxicity of Mixtures is now dealt with under Mixtures and Interaction (Section 4.3.1), which included mimicry and that on Speciation (Section 3.1.3). .Mimicry is defined and addressed in Section 2.3.3. Interactions with organic compounds are also described briefly (4.3.1). A discussion of metal complexes, including lipophilic complexes, is included in a general sense appropriate to the scope of this document (2.1, 4.3.4).

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SAB Recommendation	Action Taken
1. Executive Summary **Human Exposures and Effects (Charge questions 3.8 – 3.10)** • *Objectivity of the Discussion on Natural Background of Metals*. The SAB also recommends defining and using the terms "body burden" and "human biological monitoring" in the Framework glossary and text.	Text was added to address the risk assessment uses and implications of body burden and biological monitoring data. These data may provide key information regarding past exposure to the metal, as well as the distribution of the metal. In some cases, toxicokinetic models are available to aid in interpretation of biological monitoring data, as well as in predicting bioaccumulation and other key components of the overall toxicokinetic profile of a metal.
1. Executive Summary *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.	Executive summary comments are for the most part duplications of comments in body of document. See responses regarding specific sections below. For aquatic systems, background has been brought into the discussion of sources and releases (Section 5.2.1); trophic transfer as part of exposure analysis and bioaccumulation as a means of assessing bioavailability (5.2.5.3). Within Section 6 of the revised Framework – Terrestrial Risk Assessment for Metals, an entire subsection has been organized around a discussion of the spatial and temporal distribution of metals including natural background and heterogeneity. This section has been edited for consistency with the other sections discussing these concepts. Section 6.2.5.2 introduces the factors that influence metal bioavailability in soils as well as food web transfers.

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SAB Recommendation	Action Taken
1. Executive Summary *Ecological Exposures and Effects (Charge questions 3.11-3.14)* • *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.	Executive summary comments are for the most part duplications of comments in body of document. See responses regarding specific sections below. The revised Framework appropriately describes the limitations associated with BCFs and BAFs in terrestrial and aquatic systems.
1. Executive Summary *Ecological Exposures and Effects (Charge questions 3.11-3.14)* • *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.	The aquatic section of the revised Framework notes difficulties in the use of BAF/BCF in section 6.2.

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1. Executive Summary *Ecological Exposures and Effects (Charge questions 3.11-3.14)* • 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.	The revised Framework is not intended to provide in-depth coverage of specific tools and methods. Such treatment is viewed as more appropriate for a more technical guidance document.

1. Executive Summary *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.	The purpose of the revised Framework has been stated more clearly. It focuses on metals and metalloids and only addresses organometallic compounds with regard to the potential for transformations from inorganic compounds. Consideration was given to the title of the document. It was changed to Framework for Metals Risk Assessment.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Additional Major Revisions* • *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.	The Human Health Section has been totally rewritten and enhanced. An effort has been made to achieve better balance between the various assessment-specific sections. Aquatic and terrestrial sections followed the same general annotated outline to help insure consistency within the revised Framework.
1. Executive Summary *Additional Major Revisions* • *Restructuring of Framework Document.* The SAB recommends that Section 4 of the Framework be reorganized to mirror the organizational structure used in Section 3.	As noted above, the revised Framework represents a new structure that eliminates much of the detailed content judged more appropriate for a technical document.
1. Executive Summary *Additional Major Revisions* • *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.	Illustrative examples have been used extensively in the Human Health Section of the revised Framework.

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1. Executive Summary *Additional Major Revisions* • *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.	The revised Framework does not attempt to be comprehensive with respect to the strengths and limitations of specific tools and methods. Instead it provides examples that highlight Principles and other considerations for risk assessment. Uncertainty is discussed at a level appropriate for this framework especially with regard to the application of the Principles. This is viewed as a distinction between a Framework document and a technical guidance document.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Additional Major Revisions* • *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.*	The relevance of, and potential for, bioaccumulation is discussed in the context of toxicokinetics in the revised section on human health risk assessment (Section 4.3.4).

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Additional Major Revisions* • *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.	The human health risk assessment section within the revised Framework has been structured around the NRC paradigm of exposure assessment, hazard characterization, dose-response assessment, and risk characterization. Within each section, the presentation highlights the major considerations, with particular attention to using reference values or cancer potency factors from sources such as IRIS. The necessity of considering the relevance to the exposed population and particular exposure scenario (including frequency, duration, and exposure pathways) of the specific reference values and potency factors are also highlighted, in Section 4.2.5. Potential sensitive populations, based on life stage, health status, nutritional status, and other factors are addressed, in Section 4.2.3. Implications of uncertainties in the data and the quality of the total Risk Assessment are discussed.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Additional Major Revisions* • *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.	As noted in previous responses, the revised Framework is not intended to provide in-depth guidance. The level of guidance identified by the SAB is more appropriate for a focused technical guidance document.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
1. Executive Summary *Additional Major Revisions* • *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.	The Section on Research Needs is not considered appropriate for the revised Framework.
Overarching Comments and Recommendations 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 Human Health section has been substantially revised within the Framework, including considerable enhancement of the text, addition of a number of tables and figures, and addition of numerous references. The citations to references were updated, particularly for citations to guidance documents.
Overarching Comments and Recommendations 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.	There is no longer a toxicity testing section within the revised Framework but dietary exposures are discussed in Section 5.2.5.2. Issues and uncertainties regarding toxicity tests are mentioned in Sections 4.3.4, 4.4.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations 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.	The revised Framework reflects a substantial reorganization.
Overarching Comments and Recommendations 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 Section on Human health has been totally revised to address the SAB comments at a level appropriate for the purpose of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations 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.	Please see previous responses. The revised Framework has been restructured to highlight the Principles (Section 1.4) and to provide assessment-specific insight into how they should be considered.
Overarching Comments and Recommendations *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.	Please see previous responses related to these comments

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	Consideration was given to the title of the document. The final title is Framework for Metals Risk Assessment.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised Framework highlights Principles and other considerations for risk assessment. This is viewed as a distinction between a Framework document and a technical guidance document. This revision should provide the "identity" referred to by the SAB.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	Because the revised Framework has been structured to focus on the major Principles and other considerations, it does not attempt to be comprehensive with respect to the strengths and limitations of specific models.

Overarching Comments and Recommendations *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.	The revised Framework is not designed to provide detailed recommendations. Recommendations that are provided are focused on the applications of the Principles.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised Framework includes illustrative examples that highlight the Principles.
Overarching Comments and Recommendations *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.	The revised Framework is not intended to serve as a critique of tools and methods but rather as an overview of the key Principles and their application. Data quality and uncertainty are addressed in the risk characterization discussion, as well as in separate Agency policy.
Overarching Comments and Recommendations *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.	Several definitions have been revised.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.*	Use of the terms *"Bioaccumulation" versus "Accumulation"* have been clarified in the revised Framework and made consistent as suggested.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	See comment above, in the Executive Summary. This comment has also been addressed in Sections 4.2 and 4.3 of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised Framework provides clarifications on these terms. The revised framework describes anthropogenic sources (e.g. air deposition) and ambient sources (e.g. geology) that together comprise background. Definitions have been added for ambient and background to indicate that background = concentrations due to interaction of weather and climate on the geology and soils a particular region or site. Ambient = historical additions and natural background not influenced by current, direct releases (i.e., emissions, discharges, or disposal) from a source or site of concern. This includes metals that may arise from manmade substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that are not specifically related to the release in question (U.S. EPA, 2003c). Ambient exposure in human health has been addressed in Section 4.2.1 of the revised Framework. The implications of ambient exposure for both the development and application of reference values in human health risk assessment is discussed, in Section 4.2.5 respectively.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised framework provides definitions of terms. The forms of the metal compounds and associated processes are described within the discussion of the Principles, within the section on chemistry and, where appropriate, in the sections that address human health, aquatic, and terrestrial assessments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised Framework is not intended to provide in-depth reviews as this is viewed as more appropriate for a technical guidance document. Therefore, the level of evaluation requested by SAB is not included in the Framework. SAB's comments would be addressed in subsequent guidance. The sections within the revised Framework provide a level of detail appropriate for illustrating the Principles. The direct measurement of metal species in aquatic systems is discussed in Section 5.2.5.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The issue of mixtures is discussed in several parts of the revised Framework. The issue is introduced as one of the Principles. It is then discussed at a level appropriate for a Framework in each of the sections for human health, aquatic, and terrestrial assessments. Mixtures in the context of human health risk assessment are addressed in 4.3.1 (including the biology of the interactions and approaches for addressing mixtures are included in the risk characterization section. Toxicity issues associated with metal mixtures in aquatic systems are discussed in Section 5.3.3 Mixtures in the context of ecological risk assessment are discussed in terms of one of the key principles for metals assessment. In the context of a Framework document, metal mixtures are generally highlighted as needing explicit consideration in the risk assessment because of the unique attributes mixtures may display compared to the attributes of each individual constituent. The revised Framework reflects that individual metals exist as components of mixtures and that 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.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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).	Mimicry and the other topics mentioned are addressed in Sections 2.3.3 and 4.3.1of the revised Framework, as part of the various aspects of interactions of metals in humans.
Overarching Comments and Recommendations *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.	As noted in previous responses, the revised Framework is not intended to provide in-depth guidance. The level of guidance identified by the SAB is more appropriate for a focused guidance document. Data requirements for various approaches are beyond the scope of the revised framework

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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).	Section 3 of the revised Framework has been written around various media and provides a backdrop for the Framework. It has been shortened from the previous version and risk-related issues have been emphasized. The level of detail is considered appropriate for a Framework document in which we are trying to convey major concepts.
Overarching Comments and Recommendations *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.	The revised Framework is not intended to provide in-depth reviews as this is viewed as more appropriate for a guidance document. Therefore, the level of evaluation requested by SAB is not included in the Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations *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.	The revised Framework now includes a set of Principles that are intended to be fundamental and focused on important issues associated with assessing exposure and effects of metals.
Overarching Comments and Recommendations 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 Framework document has been revised to introduce and highlight the Principles and other common aspects for evaluating exposure and risks of metals. The Framework treats common issues up-front and then provides insights into evaluating metals for human health, aquatic, and terrestrial assessments. This structure is designed to enhance understanding by risk assessors who may be most familiar with or work in these broad areas.
Overarching Comments and Recommendations The recommendations in Section 3 of the Framework should be rewritten to clearly express them as recommendations (rather than statements).	The comment on recommendations is addressed earlier in this response.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations 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.	Please see previous responses on this topic.
Overarching Comments and Recommendations Revised recommendations in Section 3 of the Framework should not be proscriptive, but suggest options or examples.	Please see previous responses on this topic.
Overarching Comments and Recommendations 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.	Please see previous responses on this topic.
Overarching Comments and Recommendations Section 4 of the Framework should be reorganized to mirror the organizational structure used in Section 3.	Please see previous response on this topic.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Overarching Comments and Recommendations 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.	Please see previous response on this topic. The Research Needs Section is no longer in the revised Framework.
6. Response to the Charge Questions **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 compounds.** **6.1.1.1 Comments in Response to Charge Question 1.1** *Balance Between Science and Guidance* 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.	The revised Framework does not attempt to be comprehensive with respect to all details of metals and metals-related exposure and risk. Instead it highlights the Principles and provides illustrative examples. This is viewed as a distinction between a Framework document and a technical guidance document.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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 compounds.** **6.1.1.1 Comments in Response to Charge Question 1.1**	
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.	This has been approached in the revised Framework by establishing common ground for all risk assessment considerations in Section 2. This includes the Problem Formulation, Principles, Chemistry, and Conceptual Model. Assessment-specific treatments for human health and ecological are then addressed in Sections 4, 5 and 6. The team worked through common issues to identify those things that could be pulled forward as well as how to provide parallel discussions to the extent possible.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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 compounds.** **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.	The "identity" of the revised Framework is now better established. The revised Framework does not attempt to be comprehensive with respect to the strengths and limitations of specific approaches and models. Instead it provides examples that highlight Principles and other considerations for risk assessment. This is viewed as a distinction between a Framework document and a technical guidance document.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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 compounds.** **6.1.1.2 Key Recommendations in Response to Charge Question 1.1** *Long-term* 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.	See previous comments on how this has been accomplished.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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.** **6.1.2.2 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.	The assessment scale issue has been addressed in two ways within the revised Framework. First it is acknowledged at the beginning of the document. It is then discussed within Sections 4, 5, and 6 for human health and ecological assessments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *Articulation of the Inorganic Metals Assessment Principles* 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.	The discussion has been re-written within the revised Framework in the form of a set of Principles. These are then carried into subsequent discussions in Sections 4, 5 and 6.
6. Response to the Charge Questions **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** *Objectivity and Utility of Inorganic Metals Assessment Principles* • 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	As discussed in previous responses, the Principles are introduced and discussed in early sections of the revised Framework. They are then disucced again in relation to specific types of assessments. An example of how the latter is approached is provided here for Section 6 – Terrestrial Ecological Risk Assessment for Metals: 1) The major 'principles' are introduced in the first part of this Chapter with a description of the impact of the principle on terrestrial ecological risk assessments; 2) Essentiality is defined in Section 6.3 and discussed throughout the section in the context of exposure and effects in terrestrial habitats; 3) As discussed in a previous comment – background is defined as a combination of anthropogenically generated metals and ambient/natural metals. This has been clarified in Section 6.2.1. 4) Bioavailability, bioaccumulation, are discussed within the

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. • 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. 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]).	context of exposure, effects and the influence of form of the metal and soil characteristics on the bioavailability. 5) Adaptation, acclimation, and tolerance are both discussed within the context of the unique presence of ambient and anthropogenic concentrations within the soil and the impact of this 'baseline' concentration on subsequent risk calculations. Issues related to essentiality, bioavailability, and bioaccumulation in the context of human health risk assessment were in Section 4, as noted in earlier comments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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.** **6.2.1.2 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	Many of these comments have been addressed earlier in other responses. Key questions have been added throughout the document, for all sections. The Environmental Chemistry Section of the revised Framework includes a discussion of processes affecting metals in sediments. It also includes a discussion of alkylation reactions. In the terrestrial chapter, sources are discussed generally in the context of ambient and anthropogenic metals concentrations. Acclimation, adaptation and tolerance are both discussed within the context of the unique presence of ambient and anthropogenic concentrations within the soil and the impact of this 'baseline' concentration on subsequent risk calculations. Sets of Assessment Questions have been developed to assist risk assessors to think about how the Principles apply to their particular applications. The unique features of metal bioaccumulation are discussed in Sections 1.4, 2.2 of the revised Framework. Section 4.2.1 discusses adaptation and acclimation, Section 6.3.1 discusses essentiality. Sections 1.4, 2.2 and others discuss the nature and type of sources. Routes of exposure are discussed as part of waterborne and dietary exposures The human health section focuses on metal-specific issues, but provides background on general risk assessment methods in order to provide sufficient context for the metal-specific issues. Generic issues are differentiated from metal-specific issues in the text.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

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

6. Response to the Charge Questions **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.** **6.2.1.2 Key Recommendations in Response to Charge Question 2.1** *Long-term* 13. 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.	Within the revised Framework, mixtures are discussed in general in terms of the added complexity due to the unique attributes of mixtures compared to each individual metal. Challenges are discussed within the context of the various human health and ecological assessments. Metal/organic mixtures are discussed to some degree in Section 4 for human health. Mention is made in the Principles that chemical and biological processes can transform metals between inorganic and organic forms. Where appropriate, mention is made of considering organic compounds as part of mixtures as in Sections 4, 5 and 6.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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.	This has been done in the revision.

6. Response to the Charge Questions **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** *Completeness of Conceptual Model* 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.	This concept is discussed is Section 2.2 of the revised Framework. The figures have been revised.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *Linkage of Conceptual Model to Text in the Framework* 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.	The conceptual model is presented as an overview in Section 2.2. Sections on human health, aquatic, and terrestrial assessments make reference to exposure pathways as appropriate.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *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.	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: The text mentions that the distinction between dissolved and particulate forms of metals is important because reactions such as adsorption, precipitation, oxidation/reduction, and complexation control metal amounts in true solution, but not the amounts in suspension. Section 3 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. Metalloregions are presented as one example of how regional-scale risk assessment might be approached Sections 1.4 and 2.5.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *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: • 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.	The revised Framework incorporates these comments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *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: • 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.	These concepts were incorporated in the revised Framework in Sections 3, 5, and 6.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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** *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: • 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.	Metalloregions are presented as one example of how regional-scale risk assessment might be approached in Sections 1.4 and 2.5.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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.** **6.2.2.2 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.	As mentioned previously, these concepts are incorporated in the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
6. Response to the Charge Questions **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.** **6.2.2.2 Key Recommendations in Response to Charge Question 2.2** *Long-term* 1. 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. 2. An expanded description of the "metalloregions" approach of defining "metal-related ecoregions" should be incorporated into the Framework.	Metalloregions are presented as one example of how regional-scale risk assessment might be approached. Sections 1.4 and 2.5.
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? **6.3.1.2 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.	The discussion of sediment in the revised Framework has remained in the aquatic portion of the Environmental Chemistry section, while the discussion of soil has remained separate. In keeping with the purpose of the revised Framework, recommendations, if any, are minimal within the document. The Framework presents approaches that are commonly used, but does not provide direct guidance as to which approach is preferred. Human health, terrestrial and aquatic assessments are discussed in separate sections. Although there is similarity between the exposure, effects and risk analysis of metals in sediments versus soils, there are enough unique considerations that a separate discussion is warranted.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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.	Recommendations will be provided with respect to application of Principles (these are the major considerations) and not the applications of specific tools.
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 human exposure and health effects section of the Framework (Section 4) has been extensively revised to address these comments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 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 PM10 and PM2.5 need greater attention as mixtures with regard to human exposure and health effects.	Nanoparticles: See text in the response to the Executive Summary. Particulate matter, including PM10 and PM2.5: See text in the response to the Executive Summary.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Speciation: Issues related to speciation are now addressed in Sections 2 and 3 of the revised Framework. In addition, the implications of speciation for use of biomarkers and biomonitoring data are addressed in Section 3.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Dietary exposure is discussed for aquatic systems in Section 5.2.5.3 of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Biphasic dose-response: Considerations related to dose-response, and the health impacts of deficiency of essential elements are addressed in Section 4. However, since individual metals are addressed primarily in the context of highlighting broader concepts, the specifics of the lead dose-response curve were not addressed, as it is beyond the scope of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Benchmark dose modeling: The utility and advantages of Benchmark Dose modeling, particularly in the context of metals assessments, is addressed in Sections 3.1.5.2, 4.3.2, and 4.3.5.1 of the revised Framework. EPA's practice has been to update assessments based on the availability of new data and data needs, rather than re-doing modeling in the absence of a complete reassessment of the available data for the chemical. Summary tables: Have been added throughout the document. Interactions: This text has been enhanced as described in the response to the Executive Summary, although the level of detail was limited to length appropriate to a Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Summary tables have been added.

SAB Recommendation	Action Taken
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 following are examples of key items that need to be addressed. • 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.	Interactions: This text has been enhanced, as described in the response to the Executive Summary.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 also recommends that Section 4 of the Framework contain additional consideration and discussion of data requirements and model uncertainty.	The Environmental Chemistry section of the revised Framework has been reworked to provide a more concise description of important processes. Most discussions of data requirements and model uncertainty have been removed from this section in reflection of the revised focus. As discussed in previous responses, discussions of specific data requirements and uncertainties associated with particular models or approaches are not in the scope of the revised Framework.
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. **6.3.2.2 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.	These comments have already been addressed in previous responses or elsewhere in specific sections on human health, aquatic, or terrestrial assessments. The Environmental Chemistry section has been streamlined for the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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.	

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. **6.3.2.2 Key Recommendations in Response to Charge Question 3.2** *Long-term* 1. The Framework should address the importance of considering nanoparticles and their associated metal content in assessing human exposure to metals. 2. In the Framework, PM10 and PM2.5 mixtures should receive greater attention with regard to human exposure and health effects. 3. The Framework should contain more discussion of how metals interact with organic compounds, and how this interaction can lead to potentiation or antagonism. 4. 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). 5. The Framework should contain additional information on modeling issues to be considered in the marine environment (e.g., background concentrations and ion strength corrections). 6. Section 4 of the Framework should contain additional information to address model uncertainty and data requirements. 7. The Framework should contain a more explicit discussion of uncertainty in ecological risk assessment of metals. The Framework should contain a discussion of field validation needs for models.	Please see response to previous comment.

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	

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 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.	Speciation is currently addressed in a general way in Section 2.2 of the revised Framework and then in relation to specific types of assessments in Sections 4, 5, and 6. The specific points made by SAB are considered in these sections.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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.) **6.3.3.2 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.	Please see the response to the previous question as it relates to how speciation is discussed. The revised Framework does not attempt to be comprehensive with respect to all aspects of speciation models. Instead it provides examples that highlight Principles, including those related to speciation. The discussion on speciation uses the definition supplied by the SAB in Appendix B of their comments. The Environmental Chemistry section has been made shorter and more concise. The discussion on speciation includes both cations and anionic metals.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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.) **6.3.3.2 Key Recommendations in Response to Charge Question 3.3** *Long-term* 1. 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. 2. The Framework should contain a discussion of how to bound uncertainty in site and national efforts employing speciation.	See previous comment and other comments addressing the purpose of the Framework. The Environmental Chemistry section has been reworked and addresses speciation. However, these particular long-term comments have not been addressed at this time as they relate more to technical guidance.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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? **6.3.4.2 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.	Please see previous responses concerning these tables.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 toxicity assessments. See Section 4.1.2. (Emphasis added by SAB.) **6.3.5.1 Comments in Response to Charge Question 3.5** The SAB has commented on the objectivity of HSAB regarding both toxicity assessments and the broader issue of risk assessment. 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 *toxicity assessment* 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 Environmental Chemistry section of the revised Framework no longer discusses the HSAB concept with regard to toxicity. The concept of Hard Soft Acid Base has not been addressed in the human health section since alternative concepts such as, mimicry, due to size (including ionic size) and ionization potential (as a measure of binding) have wider applicability.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 toxicity assessments. See Section 4.1.2. (Emphasis added by SAB.) **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.	The Environmental Chemistry section has been reworked to address the HSAB concept without discussing toxicity. This discussion will be added to the section on HSAB. The Environmental Chemistry section has been revised and made shorter. Therefore, the addition of more citations to applications of the HSAB concept is no longer applicable. The discussion of solubility constants has been removed from the Environmental Chemistry section. The Environmental Chemistry text has been rewritten to be shorter and more concise. The specific revisions that apply to this section were made.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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.) **6.3.6.2 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., H2S(g), AsH3(g)). 5. The Framework should contain a statement concerning the potential importance of atmospheric transport to "background" concentrations of metals in the environment.	Metals in the atmosphere are now a specific part of the chemistry section in Section 3. The intent of that section is to set up major considerations regarding fate and transport that are important for risk assessments. Information specific to the scale of an assessment or to the types of receptors (human, aquatic, and terrestrial) are addressed in Sections 4, 5, and 6.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. **6.3.7.2 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 Kd 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 Kd models.	The Environmental Chemistry section has been rewritten for the revised Framework to be more concise and provide less detailed information on some topics. It is designed as a background piece for any of the assessments. It is not intended to provide a review of all the tools or a critique of their strengths and limitations.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 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.	This comment has been addressed in the section on human health assessments. Text has been added on biomonitoring and on speciation in Section 4.2, and the implications for risk assessment. This text also addresses the implications of speciation in the context of biomonitoring, although the level of detail is less than that suggested by SAB, to be consistent with other portions of the text.

SAB Recommendation	Action Taken
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** 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.	Definitions of biomonitoring and body burden have been added for the revised Framework. Some information on biomarkers and implications for risk assessment is provided in Section 4.2.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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** *Glossary* recommendation: 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. 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.	These definitions have been added for the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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). **6.3.8.2 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).	The following revisions have been made for the Framework: Ambient levels are used to refer to the combination of 'natural' background plus anthropogenic sources that are not the object of analysis. Text on body burden and human biological monitoring was added, as noted in the response to previous comments.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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). **6.3.8.2 Key Recommendations in Response to Charge Question 3.8** *Long-term* 1. 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.	Monitoring in the context of evaluating metals air emissions is discussed in Sections 3.1, 3.2 of the revised Framework. The risk assessment use of the data being collected by CDC and NHANES is addressed in the section on biomonitoring (Section 4.2 of the revised Framework).

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SAB Recommendation	Action Taken
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 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	The revised Framework discussed essentiality as appropriate for humans, other animals, and plants. A general discussion is provided when the Principles are introduced (Sections 1 and 2). Assessment-specific discussion is provided in Sections 4 through 6. The following reflects how the SAB comments have been addressed for the section on human health. The discussion of essentiality and its relationship to RDAs and RfDs has been enhanced, in Section 4.3. In addition, the text on development of RfDs has been enhanced to address issues of consistency/potential inconsistency between the RfD and RDA (4.2). The presentation of essentiality in the human health risk assessment section has been revised to focus on humans, and the list of essential metals has been revised. Tables have been added that present RDAs, RfDs, and RfCs for essential elements, and references to recent NRC reviews have been added.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
specifically reference recent U.S. Department of Agriculture (USDA) and National Research Council (NRC) reviews on essentiality of elements in humans.	

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 **6.3.9.2 Key Recommendations in Response to Charge Question 3.9** *Long-term* 1. The Framework should be revised to consider the Recommended Daily Intake for essential metals when considering Reference Doses and Reference Concentrations. 2. 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.	See the previous response; several tables have been added to the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 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	Mixture-related issues are presented in a number of places within the revised Framework. Revisions have been made to the section specific to human health risk assessment to enhance the discussion of mixtures. The material presented is at a level of detail appropriate for a Framework and is intended to alert the reader to important considerations. Detailed discussions of mixture issues are considered outside the scope of the Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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 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.	As noted in previous documents the revised Framework is not intended to identify a list of research needs. The definition of mimicry has been added to the revised Framework as part of the discussion of mixtures and interactions in Section 4.3.1, and a diagram of interactions has also been added.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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). **6.3.10.2 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.	Please see previous responses on this topic. With respect to the recommendations, the following responses are provided: 1. Interactions between organic compounds and metals are discussed in the revised Framework at a level of detail appropriate for a Framework document. 2. This example was deleted. 3. These additional subsections were added to the Mixtures discussion in Section 3.1 of the framework document. 4. Recommendations are no longer included in the Framework. However, the text on Risk Characterization will include brief text on approaches used to address mixtures and the data used to evaluate potential interactions. 5. Appropriate sections of the NRC report are cited in Section 4.3 of the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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** 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.	The revised Framework provides clarification on key concepts and terms. As noted in previous responses, the revised Framework is not intended as detailed guidance and thus does not offer extensive recommendations on what should be done for specific applications or on the strengths and limitations of tools and methods. Instead, it highlights the key issues to be considered by the risk assessor. The aquatic and terrestrial assessment sections discuss the topics at a level of detail appropriate for the framework. Bioaccumulation and trophic transfer in aquatic environments are defined and discussed in Section 5.2 of the revised Framework. The text outlines some of the difficulties in addressing trophic transfer of metals and summarizes some of the ways that bioaccumulation is expressed and measured. The section highlights considerations that are unique to metals. It does not present an evaluation of uncertainties, unknowns, or lack of informed consensus in the base of scientific support for various methods. Within the revised section on terrestrial assessments, bioaccumulation is discussed within the context of soil ingestion. The factors that impact the degree to which compounds are accumulated are also reviewed. General modeling approaches, e.g. log-linear regressions, are also introduced as examples.

SAB Recommendation	Action Taken
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** *Bioavailability* 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.	Please see the previous comment regarding the intent of the revised Framework. The following response pertains to the aquatic section of the revised Framework. According to the issue papers, aside from organic forms of selenium and mercury, the importance of trophic transfer (i.e. dietary exposures) is not clear in aquatic systems and there are currently no established procedures to assess dietary exposures of aquatic organism to metals in water quality assessments. See Sections 5.2 and 5.3. Within the revised section for terrestrial assessments, food web modeling is described in a separate subsection divided by major wildlife/exposure group including wildlife, plants and invertebrates. In these sections the importance of presence is explored. The terrestrial section focuses on soil exposures and consumptions of biota.

SAB Recommendation	Action Taken
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** *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,	Within the revised section on aquatic assessment, text has been included that identifies the problems with the use of body burdens and BAF/BCFs. This derives from the Principles and indicates that absorption, distribution, transformation, and excretion of metals depends on the metal, the form of the metal or metal compound, and the organism's ability to regulate and/or store the metal. Adverse effects of metals result when metals accumulate in target organs or tissues. Metal accumulation can apply to the entire organism, including metal adsorbed to surfaces or absorbed by the organism or to specific tissue. The section notes that bioaccumulation should be viewed a concept for use in risk assessments, particularly in the site-specific risk assessments. However, the issue of what construct to use to express bioaccumulation is separate from consideration of the bioaccumulation processes. Within the revised section on terrestrial assessment, bioaccumulation is discussed with respect to the types of species that are commonly evaluated, sources of bioaccumulation uptake factors, and the large number of uncertainties in the application of uptake models

SAB Recommendation	Action Taken
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.	

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** *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.	Please see previous responses on this topic. Additional responses are provided below. The aquatic section of the revised Framework notes that adverse effects of metals result when metals accumulate in target organs or tissues. Metal accumulation can apply to the entire organism, including metal adsorbed to surfaces or absorbed by the organism or to specific tissue. The BLM is presented as an example of an approach that relies on bioaccumulation into a particular tissue. The section also notes that in some cases (e.g. selenium) bioaccumulation measured as a whole body residue is an appropriate measure of exposure. The section further notes that the fact that body residue or critical body residue can be measured does not necessarily mean it is the concentration at the site of toxic action. See Section 5.2.5 of the revised Framework.

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SAB Recommendation	Action Taken
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. **6.3.11.2 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.	Please see previous responses on this topic. Section 5.2 of the revised section on aquatic assessment notes that bioaccumulation should be viewed as a concept for use in risk assessments, particularly in site-specific risk assessments. However, the issue of what construct to use to express bioaccumulation is separate from consideration of the bioaccumulation processes. In the revised section on terrestrial assessment, ambient and anthropogenic concentrations and their impact on 'background' levels are introduced early in the section. Recommendations are provided at a level appropriate for a Framework on how to establish ambient conditions, sources for information and generally how to arrive at background concentrations. Bioaccumulation and dietary uptake are also discussed in this section in terms of modeling approaches, uncertainties and applications. Dietary uptake is discussed in terms of an important exposure pathway/route and how diet estimates are made. Essentiality as an important baseline to consider in the effects analysis is presented as well. The section suggests making a distinction between the amounts that are required, total exposures, and incremental increases above the amounts needed by the organism, i.e. the exposure zone within which harmful effects may occur.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. 9. 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. 10. 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.	

SAB Recommendation	Action Taken
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. **6.3.12.2 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.	Please see previous responses on this topic. In particular the purpose and identity of the Framework is distinguished from an in-depth guidance document.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. **4.3.13.2 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.	The limitations of BCF/BAF approaches for national assessments is clearly stated when the Principles are introduced within the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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**	
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.	Please see previous responses with respect to the purpose of the Framework. The revised section on aquatic assessment does note that, as with toxicity tests on overlying water, sediment toxicity test methodology may not capture important processes that are occurring *in situ*. See Sections 5.2 and 5.3 of the revised Framework

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
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. **6.3.14.2 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.	Please see previous responses that have noted the revised Framework's acknowledgement of limitations of the SEM-AVS, BLM and toxicity testing methodology.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 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 (PM2.5) 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 (PM10) 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.	Please see previous responses to these issues. While inhalation is commonly considered in human health risk assessments, risk due to inhalation of airborne metals is not commonly addressed in ecological risk, usually because this is not the predominant exposure pathway. Exceptions do occur. Airborne transport of metals to terrestrial environments with subsequent exposures on leaves or surface soils is addressed within the revised Framework.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 Framework Section 3.1.2.2 - Air Pathways and Inhalation Exposure. • 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. **Addressed for HHRA – what about the other areas?**	Please see previous responses to these issues. This is addressed in the revised section on human health risk assessment.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 Framework Section 3.1.2.2 - Air Pathways and Inhalation Exposure. • 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.	Please see previous responses to these issues. This is addressed in the revised section on human health risk assessment. Risk due to inhalation of airborne metals is not typically addressed in ecological risk assessments (see previous comment response).
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 Framework Section 3.1.2.2 - Air Pathways and Inhalation Exposure. • The SAB finds that recommendation 2 (page 3-4, line 1) in Section 3.1.2.2 is appropriate as written.	Please see previous responses to these issues.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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.	The Framework has been revised to no longer include detailed recommendations. However, the concepts noted are addressed in the appropriate sections of the text.

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SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **Framework Section 3.1.2.4 - Water Pathway and Oral Exposure.** • 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.	The Framework has been revised to no longer include detailed recommendations. However, these concepts were addressed in 4.2.5.4 (exposure via water).
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **Framework Section 3.1.2.6 - Bioavailability.** • 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."	The Framework has been revised to no longer include detailed recommendations. However, the concepts noted are addressed in the appropriate sections of the text**.**

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SAB Recommendation	Action Taken

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SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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.	The Framework has been revised to no longer include detailed recommendations. RDAs and RfDs for essential metals are given and discussed in Sections 4.2 and 4.3 of the revised Framework. Essentiality is defined several times, as discussed above.

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SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **Framework Section 3.1.3.3 - Toxicity Testing.** • 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.	Please see previous responses regarding the purpose of the Framework and the level of detail that it is intended to provide. The Framework has been revised to no longer include detailed recommendations. However, the concepts noted are addressed in the appropriate sections of the text. These points were noted in the discussion on human variability in Sections 4.2 and 4.3.

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SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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." - 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	Please see previous responses on these issues. With respect to human health assessments, the issue of metals-organic mixtures are discussed in Section 4.4 on risk characterization. The NAS/NRC mixtures document is referenced. The revised Section 5 on aquatic assessment addresses additivity, potentiation and antagonism.

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SAB Recommendation	Action Taken
mechanism of action for metals. Future research goals should determine how considerations of metal mimicry may affect risk assessments and metal toxicity."	
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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)."	The Framework has been revised to no longer include detailed recommendations. However, populations with differing sensitivity/susceptibility are addressed in Section 4.2.3.
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **Framework Section 3.2.3 - Background.** • 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.	Please see previous responses on this issue.

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SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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.	Please see previous responses on this issue. In addition, effects of dietary exposure in aquatic systems are discussed in Section 5.2 of the revised Framework.
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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."	Please see previous responses regarding dietary exposure and trophic transfer

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

SAB Recommendation	Action Taken
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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.	Please see previous responses on this issue.
Appendix A. Detailed Comments and Suggested Technical Corrections in Response to Charge Question 3.1 **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."	Please see previous responses regarding approaches to human health mixtures risk assessment.
Appendix C. Suggested Editorial/Wording Changes ***Section 2 of the Framework*** • 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.	Key factors affecting the conceptual model have been listed.

Summary Table – EPA Response to SAB Recommendations for Metals Framework and Actions Taken

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

Appendix C. Suggested Editorial/Wording Changes ***Section 2 of the Framework*** • 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.	These corrections and suggestions have been addressed in the revised Framework. Mg, Si, W, U, Te were addressed in Table 4-1. Magnesium was addressed under Essential Metals, Section 4.1. Chromium references were used as relevant.