1. INTRODUCTION

Inorganic metals and metal compounds have unique characteristics that should be considered when assessing their risks. Some of these characteristics typically are not considered when assessing the risks of organic substances. For example, metals are neither created nor destroyed by biological or chemical processes; they are transformed from one chemical form to another. Native (zero valence) forms of most metals and some metal compounds are not readily soluble, and as a result, toxicity tests based on soluble salts may overestimate the bioavailability and toxicity of these substances. Some metals (e.g., copper [Cu], selenium [Se], and zinc[Zn]) are nutritionally essential elements at low levels but toxic at higher levels, and others (e.g., lead [Pb], arsenic [As], and mercury [Hg]) have no known biological functions. Because metals are naturally occurring, many organisms have evolved mechanisms to regulate accumulations, especially accumulations of essential metals. This metals risk assessment Framework identifies metals principles that are fundamental truths (or properties) of metals. The metals principles should be addressed and incorporated into inorganic metals risk assessments.

Metals Principles

- Metals are naturally occurring constituents in the environment and vary in concentrations across geographic regions.
- All environmental media have naturally occurring mixtures of metals, and metals are often introduced into the environment as mixtures.
- Some metals are essential for maintaining proper health of humans, animals, plants, and microorganisms.
- The environmental chemistry of metals strongly influences their fate and effects on human and ecological receptors.
- The toxicokinetics and toxicodynamics of metals depend on the metal, the form of the metal or metal compound, and the organism's ability to regulate and/or store the metal.

Because the majority of compounds assessed by the United States Environmental Protection Agency (EPA or the Agency) are organic substances, the various guidance documents provided for risk assessments of either human health or ecological receptors lack specificity on how to account for these and other metal attributes. This document attempts to fill this gap in current guidance.

1.1. PURPOSE AND AUDIENCE

The primary purpose of the Framework for Metals Risk Assessment is to identify key principles that should be addressed in any inorganic metals analysis and to provide EPA program offices and regions with guidance on how to consider these principles in EPA risk assessment practices. Although the primary audience will be Agency risk assessors, the Framework will also communicate these principles to stakeholders and the public. The Framework relies on the draft Framework document, the issue papers, and Science Advisory Board (SAB) comments. The issue papers were developed, under EPA commission, to address key scientific topics pertaining to inorganic metals. The papers are available on EPA's Web site at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119, which includes links to the draft framework (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=88903). The SAB's comments are available at http://www.epa.gov/sab/pdf/metals_sab-06-002.pdf.

This Framework document has been developed to supplement previous guidance for use in site-specific risk assessments; criteria derivation, ranking, or categorization; and other similar Agency activities related to metals. The Framework is not a prescriptive guide on how any particular type of assessment should be conducted within an EPA program office. It is, however, intended to address issues that are unique to metals and frequently encountered when conducting a metals-specific risk assessment. This document does not address issues and methods that are common for both metals and organic compounds nor does it develop further guidance on issues that remain controversial or unresolved for assessments of risks from chemicals in general. Information on general risk assessment topics is available on EPA's Web site at http://cfpub.epa.gov/ncea/ and http://cfpub.epa.gov/ncea/raf/index.cfm.

The Framework is intended to be used for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no binding effect on EPA or any regulated entity. Rather, it represents a nonbinding statement of policy. EPA believes that the Framework provides a sound, up-to-date presentation of principles; provides guidance on how to consider these principles in assessing the risk posed by metals; and enhances application of the best available science in Agency risk assessments. However, EPA may conduct metals risk assessments using approaches that differ from those described in the Framework for many reasons, including, but not limited to, new information, new scientific understandings, and new science policy judgments. While the science surrounding metals risk assessment continues to be studied intensively and is evolving rapidly, some areas still lack sufficient information for a quantitative assessment. Thus, specific approaches may become outdated or may otherwise require modification to reflect the best available science and others may be addressed only qualitatively until additional information becomes available. Application of this Framework in future metals risk assessments will be based on EPA decisions that its approaches are suitable and appropriate. These judgments will be tested and examined through peer review, and any risk analysis will be modified as deemed appropriate.

1.2. METALS FRAMEWORK SCOPE

The Agency regulates metals and their inorganic and organometallic compounds (compounds exhibiting properties of both organic and metal compounds) because they have the potential to harm human health and the environment. The Agency's SAB has stressed the importance of environmental chemistry and its relevance to the assessment of both inorganic and organometallic compounds. However, the complexities of addressing all types of metal compounds within a single document would result in a framework that would be difficult to follow or to apply in specific cases. Because organometallic compounds exhibit properties common to both organic substances and metal compounds, the properties of both the organic moieties of these compounds and their components would need to be addressed. EPA has already developed frameworks and associated guidance documents for assessing properties of organic compounds. Therefore, this document addresses only the assessment issues associated with inorganic metal compounds. The Framework does discuss natural transformation pathways that form organometallic compounds and refers the reader to appropriate Agency documentation or research efforts related to relevant risk assessment issues.

Metals and Metalloids of Primary Interest

Aluminum	Manganese
Antimony	Mercury (inorganic)
Arsenic	Molybdenum
Barium	Nickel
Beryllium	Selenium
Boron	Silver
Cadmium	Strontium
Chromium	Tin
Cobalt	Thallium
Copper	Vanadium
Iron	Zinc
Lead	

In this Framework, the term "metals" refers to inorganic metals and metalloids that may pose a toxic hazard and are currently of primary interest to EPA. However, the principles and approaches set forth in the Framework are applicable to all metals. In some instances, metal-by-metal considerations are included, either as examples or as ways to highlight particular exceptions. Furthermore, in some cases, this document may discuss particular tools or methods that expand on a particular principle and its consideration in the context of EPA hazard and risk assessment. The discussions are intended to be illustrative and are not intended to provide a complete description of the applications and limitations of any particular tool or method, although proper citations to the open scientific literature are included. Nor does the Framework provide an exhaustive summary of all the tools and methods available to risk assessors, as this type of analysis is beyond the scope of this document.

1.3. METALS ASSESSMENT CONTEXT

The context for the risk assessment is a major factor in determining the type of analysis appropriate for any particular situation. The Agency conducts a variety of assessments, from site-specific risk assessments to national criteria setting and ranking. To provide a context for discussion of the Framework principles for metals, this document has defined three general categories of metals assessments: national ranking and categorization, national-level assessments, and site-specific assessments. (See Figure 1-1 identifying the three categories of assessment in the context of the Agency's statutory authority.) As shown in the figure, national-scale and site-specific assessments can vary in level of detail—from simple screening analyses to complex definitive assessments. For example, in conducting a national-level screening analysis, EPA might undertake a screening-level review of a pesticide or new chemical under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) or the Toxic Substances Control Act (TSCA), and this may lead to a more definitive assessment if the screen cannot rule out a threat to health or the environment. Site-specific screening-level assessments might be sufficient to support an environmental impact statement, and a more complex analysis might be necessary as a part of a Superfund cleanup action. All three categories of assessments share common elements and rely on accurate information and knowledge about how metals behave in the environment and when they come into contact with humans or other organisms of concern. Metals have unique environmental and toxicological properties that may confound such assessments if they are not given consideration. Each of the three general assessment categories is discussed in more detail below.

1.3.1. National Ranking and Categorization

EPA may rank or categorize some chemicals based on their potential to cause risk to human health or the environment. Although there continue to be gaps in data to understanding the chemistry, environmental behavior, toxicity, and exposure potential for many chemicals, EPA is tasked with protecting and mitigating exposures and harmful effects associated with exposure to these chemicals. The Agency often is in a position, despite imperfect and incomplete databases, where methods and tools need to be developed to identify, characterize, and in some cases, rank and categorize chemicals.

With more than 80,000 chemicals currently listed on the TSCA inventory that can legally be used in commerce within the U.S. (not including pesticides or chemicals that are created as byproducts during industrial processes), the Agency needs a way to prioritize substances for review or action. Many of the statutes administered by EPA provide specific lists of chemicals that require consideration, but often those lists are based on information and analyses previously developed by EPA. In addition, the statutes generally provide for adding or deleting chemicals from the initial list on the basis of their potential threat to human health or ecological receptors. Consequently, a need exists for methods that rapidly screen chemicals for placement on lists or that prioritize potentially hazardous substances.

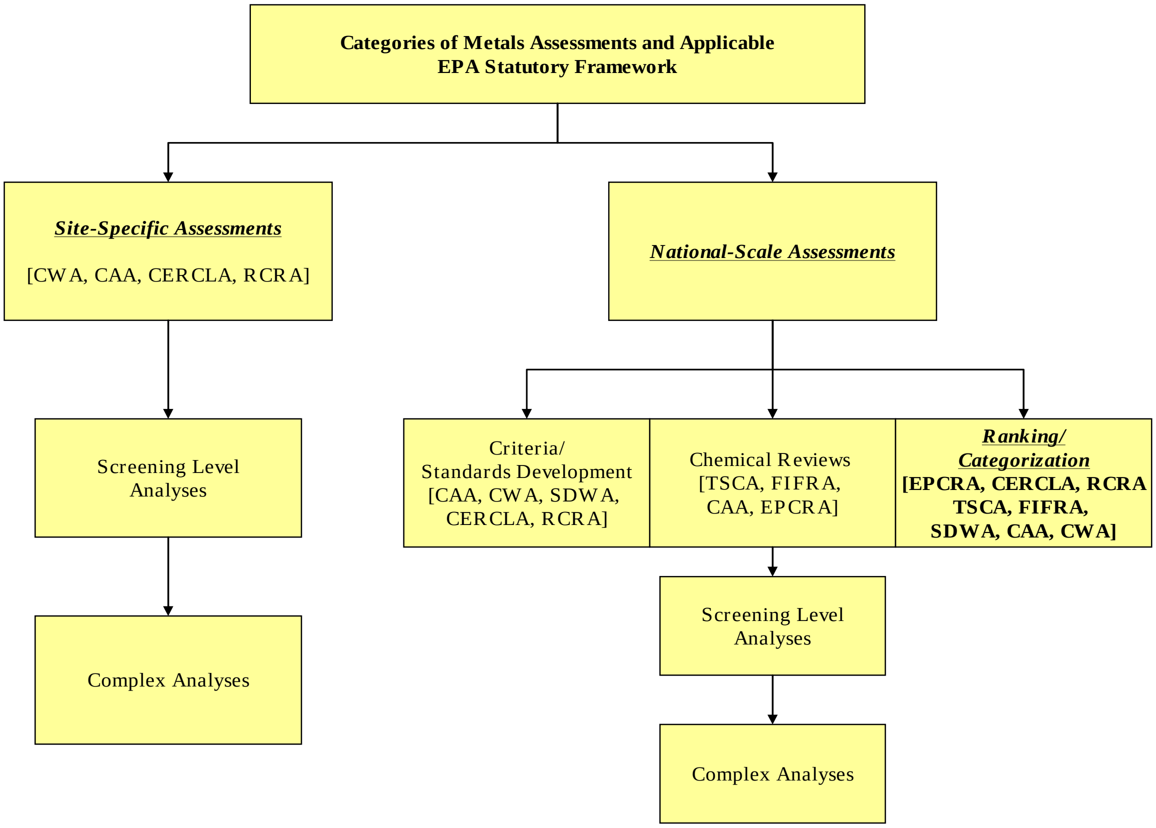

Figure 1-1. Categories of metals assessments under EPA statutory framework.

Some of the ranking and categorization methods used by EPA involve identifying certain attributes of chemicals that can then be used as indicators of potential human health or ecological risk. Example attributes include human and ecological toxicity, production volume, quantities released to the environment, persistence in the environment, mobility in the environment as indicated by volatility or solubility, and potential to bioaccumulate in the food chain. Other methods, which may be less quantitative, rely more on a combination of expert judgment, stakeholder input, and availability of information to determine the priority or categorization of chemicals for decision making or other action. Examples of programs where EPA identifies or categorizes chemicals for priority action based on human health or ecological concerns include the following:

- Selecting chemicals for the Agency's Toxicity Characteristic regulation (40 CFR 261.24) that defines hazardous wastes
- Establishing reporting thresholds for spills of hazardous materials under Superfund
- Setting priorities for revisions to the Ambient Water Quality Criteria (AWQC)

- Listing chemicals under the Toxics Release Inventory
- Determining priorities for developing drinking water standards
- Setting priorities for hazardous air pollutant data collection and assessment, and
- Setting priorities for reviewing existing chemicals under TSCA.

This list of needs for ranking or categorizing chemicals is not comprehensive but is illustrative of the activities that EPA conducts in this regard. In addition, the Agency may set national standards and guidelines for specific chemicals, including metals, as described in the next section.

Ambient Water Quality Criteria

EPA's Office of Water is charged with developing Ambient Water Quality Criteria (AWQC) to support the Clean Water Act goals of protecting and maintaining the physical, chemical, and biological integrity of U.S. waters. Examples of chemical-specific criteria include those designed to protect human health, aquatic life, and wildlife. Although AWQC are typically derived at a national level, there is a long history behind the development of methods to accommodate site-specific differences in metals bioavailability. For example, since the 1980s, aquatic life criteria for several cationic metals have been expressed as a function of water hardness to address the combined effect of certain cations (principally calcium and magnesium) on toxicity. Recognizing that water hardness adjustments did not account for other important ions and ligands that can alter metals bioavailability and toxicity, EPA developed the water effect ratio (WER) procedure as an empirical approach for making site-specific bioavailability adjustments to criteria (U.S. EPA, 1994a). This approach relies on comparing toxicity measurements made in site water with those made in laboratory water to derive a WER. The WER is then used to adjust the national criterion to reflect site-specific bioavailability. More recently, the Office of Water has been developing a mechanistic-based approach for addressing metals bioavailability using the Biotic Ligand Model (BLM) (Di Toro et al., 2001; Santore et al., 2001; U.S. EPA, 2000b). This model, discussed in Chapter 5, predicts acute toxicity to aquatic organisms on the basis of physical and chemical factors affecting speciation, complexation, and competition of metals for interaction at the biotic ligand (i.e., the gill in the case of fish). The BLM has been most extensively developed for copper and is being incorporated directly into the national copper aquatic life criterion. The BLM is also being developed for use with other metals, including silver. Conceptually, the BLM has appeal because metals criteria could be implemented to account for predicted periods of enhanced bioavailability at a site that may not be captured by purely empirical methods, such as the WER.

1.3.2. National-Level Assessments

National-level assessments may be performed when the Agency is setting media standards or guidelines for chemicals (e.g., Maximum Contaminant Levels [MCLs], National Ambient Air Quality Standards, AWQC, Superfund soil-screening levels) or when the Agency is using risk assessments to establish controls for environmental releases from industry or other sources (e.g., hazardous waste listings under the Resource Conservation and Recovery Act, residual risk determinations under the Clean Air Act, and pesticide registrations). These assessments can vary in level of detail from simple, screening analysis to complex, data-intensive definitive assessments. EPA also is charged with establishing controls on environmental releases based on the best available treatment technologies (e.g., maximum achievable control technology for air emission and best available treatment technology for surface water discharges and for hazardous wastes). However, even though the standards are based on technological achievability, the Agency typically performs risk assessments in support of these regulations to help inform management decisions and for use in cost/benefit analyses.

Differing environmental conditions across the country affect the biogeochemistry of metals, making it difficult to set single-value national criteria that represent the same risk level across the whole country (national standards that apply at the point of exposure, such as MCLs, are less affected by these factors). To conduct such assessments, the Agency commonly undertakes several approaches. One is to define one or more exposure scenarios and to conduct a relatively detailed analysis. The difficulty in this approach is in selecting the appropriate scenario; typically, the Agency tries to ensure that the scenario is sufficiently conservative to be protective of the population at highest risk (such as populations exposed above the 90th percentile) without being so conservative that the standards are protective of hypothetical individuals whose calculated risks are above the real risk distribution. In selecting the appropriate scenario, the Agency needs to consider all the factors that may affect potential risk, including environmental factors affecting the fate, transport, exposure potential, and toxicity of the chemicals released.

Hazardous Waste Listing Determination

Under the Resource Conservation and Recovery Act, EPA is required to make formal decisions on whether to designate certain specific industry waste streams as hazardous. For waste streams that are listed as hazardous, the generators and handlers of those wastes must comply with a comprehensive set of management and treatment standards. In determining whether to list a waste as hazardous, the Agency evaluates the ways in which that waste is currently being managed or could plausibly be managed by the generators and handlers of the waste. The Agency also assesses the physical and chemical composition of the waste. Based on the waste characteristics and management practices, EPA then conducts an analysis to determine whether potentially harmful constituents in the waste might be released and transported to human or ecological receptors. In conducting these analyses, the Agency evaluates the potential for constituents in the waste material to be released to air, surface water, soil, and ground water. It then models the fate and transport of those constituents to potential receptors.

Another common approach for a national assessment or criteria derivation is to conduct a probabilistic analysis (such as a Monte Carlo analysis), wherein the variability of the key factors is described by parameter distributions used as inputs to the probability analysis procedure. The result is an integrated distribution of potential risk levels. The difficulties related to conducting this kind of analysis are in developing appropriate distributions for each parameter and in ensuring that adequate attention is paid to potential correlations among key parameters. These correlations often are more complex and difficult to describe for metals than for organic compounds.

1.3.3. Site-Specific Assessments

Site-specific assessments are conducted to inform a decision concerning a particular location and may also support some national regulatory decisions. They can also vary in detail from screening-level to complex, definitive-level analyses.

- Determining appropriate soil cleanup levels at a Superfund site
- Establishing water discharge permit conditions to meet AWQS, and
- Determining the need for emission standards for sources of hazardous air pollutants.

Establishing Water Discharge Permit Conditions

The Clean Water Act establishes a two-tier process for setting water discharge permit conditions. First, all dischargers must meet the technology-based effluent guidelines limitations requirements. Second, if those limitations are not adequate to allow the receiving stream to achieve its designated water quality standards (WQS), then more stringent limits are developed to ensure that those standards are met. WQS are established by the states and consist of a designated use for the water body and a set of criteria for individual chemicals that allow that use to be achieved. EPA has published national water quality criteria values for the states to use as guidance in setting their standards.

Once the standards that include the criteria have been established and it has been determined that the effluent guidelines alone will not be sufficient to allow those criteria to be met, the state prepares a wasteload allocation for all the dischargers to that stream segment, including, where appropriate, the nonpoint source discharges. The wasteload allocation generally consists of modeling the potential impact on the stream from each discharge of the chemicals of concern and then setting the allowable discharges to ensure that the criteria for the chemicals are met. The modeling process can be quite complex, potentially taking into account the interactions of the ambient stream conditions with the chemicals in the discharge, including dilution, chemical transformations, degradation, settling, resuspension, and other processes. For metals, stream characteristics such as pH, organic content, suspended solids levels, and numerous other factors can significantly affect how the metal will behave and affect aquatic life in the stream segment. Therefore, it is important to understand these processes in conducting the wasteload allocation.

An accurate site-specific assessment for an inorganic metal requires knowledge of the form (or forms) of the metal as it enters the environment, the environmental conditions affecting the metal (climatological conditions, soil geochemistry, water and sediment chemistry, etc.), the existence of plants and/or animals in which the metal might bioaccumulate as well as the uptake factors for whatever form(s) the metal may be in, plausible pathways and routes of exposures to the human or ecological receptors, and the effect the metal will have on target organisms in whatever form in which it reaches that organism and its target organ/system. Although many of these same principles also affect the risk potential of organic chemicals, models for predicting fate, transport, and toxic properties are generally better defined for organic chemicals than for metals.

1.4. KEY PRINCIPLES TO CONSIDER IN METALS RISK ASSESSMENT

One of the purposes of this Framework is to present key principles that differentiate inorganic metal compounds from other chemicals. These key principles, defined in subsequent subsections, warrant careful consideration when assessing the risks to human health and the environment associated with exposures to metals or metal compounds and should be addressed and incorporated into metals risk assessments to the extent practicable. For example, it is known that certain metal compounds bioaccumulate in human tissues and that this bioaccumulation can be related to the metals' toxicity (SAB, 2006). Contributors to the Metals Action Plan (MAP), members of the SAB, and external stakeholders, along with various contributors to and authors of this Framework, have discussed these metals principles for consideration in the assessment of metals. They are visible throughout this document. In Chapter 2, they are broadly discussed in the context of the Agency's risk assessment process. In Chapters 4 through 6, they are discussed in the context of human health, aquatic, or terrestrial risk assessment processes. The remainder of this chapter discusses these principles in more detail, focusing on the unique properties of metal compounds and why these principles are important for metals risk assessments.

1.4.1. Metals are Naturally Occurring Constituents in the Environment and Vary in Concentrations Across Geographic Regions

Implications for risk assessment include the following:

- Humans, other animals, and plants have evolved in the presence of metals and are adapted to various levels of metals. Many animals and plants exhibit geographic distributions that reflect variable requirements for and/or tolerance to certain metals. These regional differences in requirements and tolerances should be kept in mind when conducting toxicity tests, evaluating risks, and extrapolating across regions that differ naturally in metals levels.

- As a result of industrialization, current levels of metals may be elevated relative to levels occurring naturally. Depending on the purpose of the risk assessment, care should be taken to understand and distinguish among naturally occurring levels, current background levels (i.e., natural and anthropogenic sources), and contributions to current levels from specific activities of concern.

- Because the diets of humans and other animals are diverse, there may be wide variability in the dietary intake of some metals (e.g., in seafood), resulting in both temporal variability (e.g., spikes after a seafood meal or with life stage) and geographic or cultural variability.

1.4.2. All Environmental Media have Naturally Occurring Mixtures of Metals and Metals are Often Introduced into the Environment as Mixtures

Implications for risk assessment include the following:

- Some metals act additively when they are present together, others act independently of each other, and still others are antagonistic or synergistic. Such interactions are important aspects of assessing exposure and effects.

- Interactions among metals within organisms may occur when they compete for binding locations on specific enzymes or receptors during the processes of absorption, excretion, or sequestration, or at the target site.

- The presence of and amount of other metals are important when conducting and interpreting laboratory tests.

1.4.3. Some Metals are Essential for Maintaining Proper Health of Humans, Animals, Plants, and Microorganisms

Implications for risk assessment include the following:

- Adverse nutritional effects can occur if essential metals are not available in sufficient amounts. Nutritional deficits can be inherently adverse and can increase the vulnerability of humans and other organisms to other stressors, including those associated with other metals.

- Excess amounts of essential metals can result in adverse effects if they overwhelm an organism's homeostatic mechanisms. Such homeostatic controls do not apply at the point of contact between the organism and the environmental exposure.

- Essentiality thus should be viewed as part of the overall dose-response relationship for those metals shown to be essential, and the shape of this relationship can vary among organisms. For a given population, "reference doses" designed to protect from toxicity of excess should not be set below doses identified as essential. Essential doses are typically life-stage and gender specific.

1.4.4. The Environmental Chemistry of Metals Strongly Influences Their Fate and Effects on Human and Ecological Receptors

Unlike organic chemicals, metals are neither created nor destroyed by biological or chemical processes. However, these processes can transform metals from one species to another (valence states) and can convert them between inorganic and organic forms. Metals also are present in various sizes, from small particles to large masses. Implications for risk assessment include the following:

- The form of the metal (chemical species, compound, matrix, and particle size) influences the metal's bioaccessibility, bioavailability, fate, and effects.

- The form of the metal is influenced by environmental properties, such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides.

- Certain forms of metals are used for evaluating exposure and effects. For example, the free metal ion is used for exposure assessments based on competitive binding of metal to specific sites of action.

- Metals attached to small airborne particles are of primary importance for inhalation exposures, although a few metals and metal compounds may exist as vapors (e.g., mercury).

- Information developed on the fate and effects of one form of a metal may not be directly applicable to other forms.

- Organometallic forms have different characteristics from inorganic metals and metal compounds, and the same general principles and approaches for risk assessment do not apply.

1.4.5. The Toxicokinetics and Toxicodynamics of Metals Depend on the Metal, the Form of the Metal or Metal Compound, and the Organism's Ability to Regulate and/or Store the Metal

These processes are often highly dynamic (e.g., vary according to exposure route and concentration, metal, and organism) and thus exert a direct influence on the expression of metal toxicity. Implications for risk assessment include the following:

- Certain metal compounds are known to bioaccumulate in tissues and this bioaccumulation can be related to their toxicity.

- The latest scientific data on bioaccumulation do not currently support the use of bioconcentration factor (BCF) and bioaccumulation factor (BAF) values when applied as generic threshold criteria for the hazard potential of inorganic metals in human and ecological risk assessment (e.g., for classification as a persistent bioaccumulative toxic [PBT] chemical).

- Single value BAF/BCFs hold the most value for site-specific assessments when extrapolation across different exposure conditions is minimized.

- For regional and national assessments, BAF/BCFs should be expressed as a function of media chemistry and metal concentration for particular species (or closely related organisms).

- Trophic transfer can be an important route of exposure for metals, although biomagnification of inorganic forms of metals in food webs is generally not a concern in metals assessments.

- Kinetic-based bioaccumulation models (e.g., DYNBAM) have been shown to accurately describe bioaccumulation resulting from different exposure routes for various metals and aquatic organisms and should be considered as alternatives to the BCF/BAF approach when appropriate data are available.

- Many organisms have developed physiological or anatomical means for regulating and/or storing certain metals up to certain exposure levels such that metals may not be present in organisms in a concentration, form, or place that can result in a toxic effect.

- The organ or tissue in which metal toxicity occurs may differ from the organ or tissue(s) in which the metal bioaccumulates and may be affected by the metal's kinetics. Target organs may differ by species, mainly owing to differences in absorption, distribution, and excretion. Effects at the portal of entry to an organism are less dependent on kinetic processes internal to an organism.

- Both the exposure route and the form of a metal can affect the metal's carcinogenic potential (assessed in the context of human health risk assessment) and its noncancer effects.

- Sensitivity to metals varies with age, sex, pregnancy status, nutritional status, and genetics (due to genetic polymorphisms).