2. FRAMEWORK FOR METALS RISK ASSESSMENT

The following discussion addresses issues that are unique to inorganic metals and routinely encountered during the inorganic metals risk assessment process. Discussions of issues generic to any chemical risk assessments are kept to a minimum because these are dealt with in other framework and guidance documents (e.g., U.S. EPA, 2003a, 2000a, 1998a; http://www.epa.gov/ncea/ and http://www.epa.gov/ncea/raf).

This chapter provides an overview of the risk assessment phases and assessment questions. Environmental chemistry issues and their implication in the assessment of inorganic metals are also discussed. The chapter is organized around the overall risk assessment paradigm. (See Figure 2-1, which broadly illustrates the overall risk assessment/risk management process and identifies some metals-specific considerations in the problem formulation and analysis steps.) An effective risk assessment for metals will account for the unique aspects of metals that differentiate them from other substances early and throughout the risk assessment process.

For assessments of human health or ecological risks at national, regional, or site-specific scales, the metals principles can be translated into sets of assessment questions. As appropriate, the risk assessor can use these questions to meet the needs of the assessment. The risk assessor should consider these questions throughout the risk assessment process; however, they are especially important in focusing the assessment during the Planning and Problem Formulation phase. Suggested assessment questions are given within this Framework for Problem Formulation, Analysis, and Risk Characterization. These questions are not exhaustive but provide the risk assessor with a feel for the proper questions to ask.

2.1. HUMAN HEALTH AND ECOLOGICAL RISK ASSESSMENT: PLANNING AND PROBLEM FORMULATION

Planning and Problem Formulation are critically important for both human health and ecological risk assessments (U.S. EPA, 2003a, 2000a, 1998a). The concepts embodied in Planning and Problem Formulation are valuable starting points for any risk assessment involving metals. Planning and Problem Formulation provide an opportunity for initial consideration of the metals' characteristics and their chemistry. These considerations, along with other aspects of the assessment, contribute to the development of a conceptual model that conveys the important elements of the metals risk assessment.

Although Problem Formulation is not explicitly included in the human health risk assessment (HHRA) paradigm, as it is in the ecological risk assessment guidelines, current practice is to consider many of the issues in the planning stages that the assessor anticipates will be incorporated later in the HHRA. This is particularly true for more complex assessments that

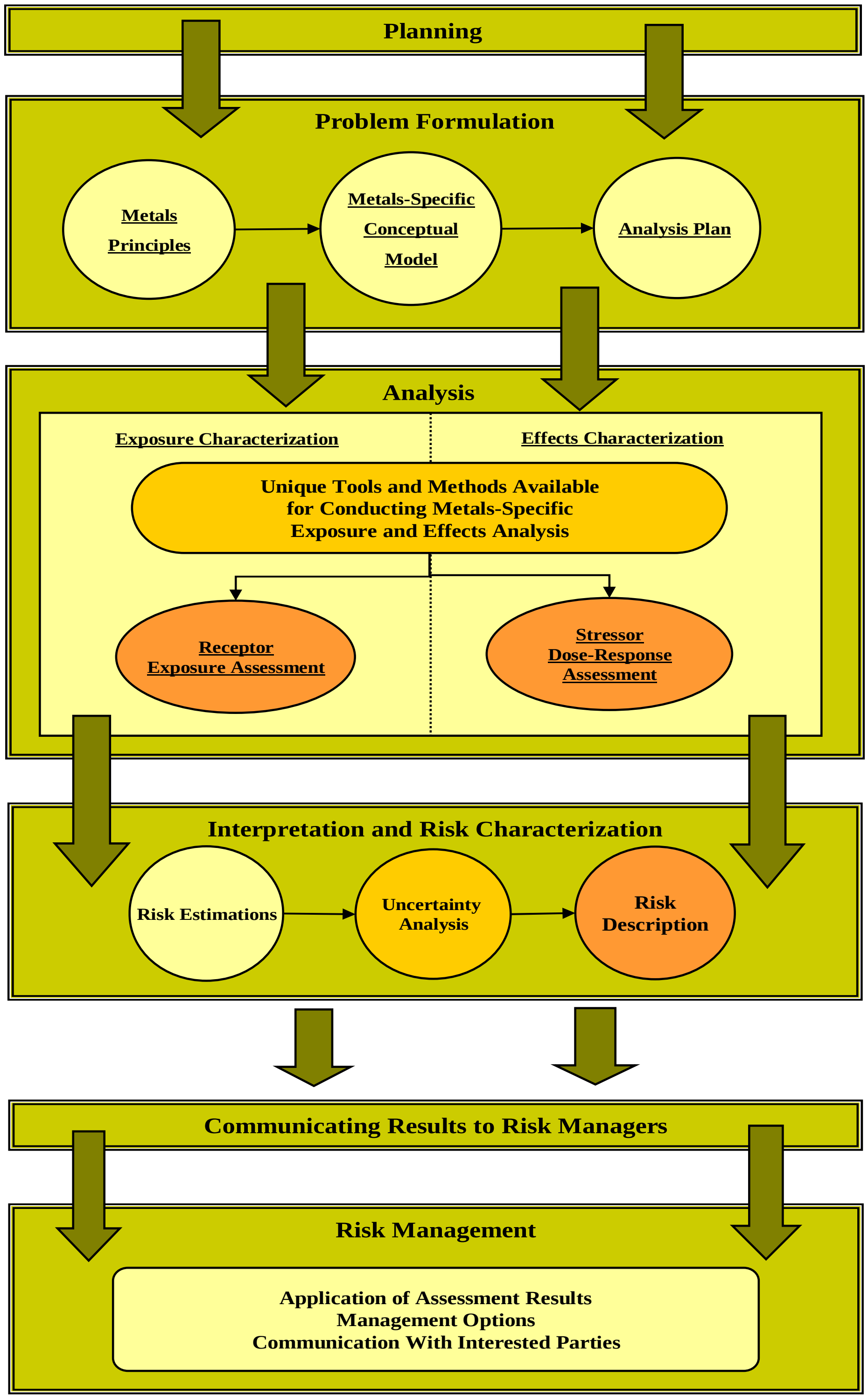

Figure 2-1. Risk assessment/risk management process for metals.

consider multiple metals, pathways/routes of exposure, etc., as is advised in EPA's Framework for Cumulative Risk Assessment (U.S. EPA, 2003e). These planning and scoping activities may include

- defining the geographic scale and scope (site, national-scale, etc.) of the assessment
- identifying potentially exposed populations and sensitive subpopulations
- characterizing exposure pathways and exposure routes (conceptual model)
- describing how exposure will be assessed
- determining how hazard and the receptor's dose-response will be assessed, and
- describing how risks will be characterized.

For metals, the type of assessment (i.e., screening or detailed) and the scale of the assessment (i.e., site specific, regional, or national) will determine how information on metals can be applied in the assessment. Site-specific assessments will involve only a single geographical area of concern and, therefore, can incorporate locally relevant aspects of environmental chemistry, background concentrations, and species sensitivities. For regional and national-scale assessments, more general assumptions about the form of the metal in the environment, deposition pathways, uptake and bioavailability parameters, and sensitive species or subpopulations are useful. These general assumptions frequently produce results that are conservative in their assumptions in an effort to be protective of sensitive species or locations. Regardless, the key principles in metals risk assessment should be considered in all risk assessments.

Translating the Metals Assessment Principles into Assessment Questions

Translating the metals principles into assessment questions should be stressed during planning and problem formulation. This step helps ensure that the principles have been appropriately considered.

For metals risk assessment, the risk assessor should consider the following examples of questions that should be considered during the planning and scoping of the Problem Formulation phases:

Background Concentrations

- How should background (natural and anthropogenic) levels for metals be characterized for the selected spatial scale of the assessment?
- Is ecoregion-specific information available or is the use of state averages, or distributions, compatible with the level of ecological relevance and certainty required by the risk analysis?
- For ecological risk assessments, are acclimation, adaptation, and tolerance data for organisms of concern available and are these issues being considered?

Mixtures and Interactions

- How will interactions affecting uptake and systemic effects be considered?

- Will issues be considered such as reduction of reactivity and increase in mobility by organic compounds that form complexes with metals and possible increases in toxic effects of organic compounds that form lipophilic complexes with metals?

- Will interactions with other metals and with organics (e.g., As and polycyclic aromatic hydrocarbons) be addressed?

Essentiality

- Are nutritional deficits, which can be inherently adverse and can increase the vulnerability of humans and other organisms to other stressors, be included in the assessment?

- How will both toxicity and deficiencies of essential metals be characterized?

Forms of Metals

- Since environmental chemistry is a primary factor influencing metal speciation and subsequent transport, uptake, and toxicity, how will it be included in the risk assessment?

- How will environmental conditions (e.g., pH and oxidation-reduction reactions) be addressed to determine metal speciation and mobility?

Toxicokinetics/Toxicodynamics of Metals

- What metal-related responses are of most concern in the health risk assessment?

- Which sensitive subpopulations should be considered for each metal of concern?

- How will biotic and abiotic factors that influence the bioavailability and bioaccumulation of metals be incorporated into the risk assessment?

- How will environmental factors that affect metal speciation and metabolic capacity of biota to regulate internal metal concentrations (homeostatic controls) be accounted for when calculating the bioaccumulation potential of metals?

2.2. METALS CONCEPTUAL MODEL

The relationships between the sources, exposure, and effects of metals to human and ecological receptors are complex and often are specific to a particular site, environmental condition, and receptor organism. Because metals are naturally occurring substances that undergo extensive biogeochemical cycling (i.e., are not destroyed but change form), transition functions between environmental loadings, media concentrations, exposed receptors, and the final organismal or ecosystem responses are affected by natural processes to a much greater extent than those that occur with xenobiotic organic contaminants. The assessor should identify these transition functions in the conceptual model for all metals assessments.

The generic conceptual model depicted in Figure 2-2 shows the interrelationship between the metals or metal compounds of interest and the health risk assessment process. It is a representation of the actual and potential, direct and indirect relationships between stressors in the environment and exposed humans (or particular subpopulations) or ecological entities. The conceptual model depicts possible pathways from sources of metals and typical ways in which risk is assessed (e.g., on the basis of media concentrations, calculated dose, or residues in tissues). This model follows the same format as a typical chemical assessment, but it identifies areas (primarily in the transition states between environmental compartments) where metal-specific issues require additional consideration. For simplicity, the numerous environmental or biological processes that influence the predominant route of exposure or the physical/chemical properties of the metal compounds are not depicted in this model, but such processes would be used as inputs to models developed for specific assessments. The bidirectional arrows represent the fact that the transition functions (models) can be applied in a prospective manner (i.e., in a left-to-right direction to determine risks associated with a given load or exposure) or in a retrospective manner (in a right-to-left direction to determine the load or exposure associated with a predetermined level of risk). The latter is usually done for generating human and ecological quality criteria expressed as media concentrations.

The goals and scope of a health risk assessment, in addition to the availability of data, methods, and resources, are among the most important factors that determine the extent to which the key principles specific to metals (given in Section 1.4) can be incorporated into an assessment. Generally, health risk assessment endpoints are selected during the Problem Formulation phase of a risk assessment based on their relevance to risk management goals, societal values and laws, known adverse effects of metals, and endpoints of importance to stakeholders. Risk assessors will incorporate the metals principles to a lesser extent in screening-level assessments than in detailed risk assessments. Site-specific assessments can account for more metal-specific processes (particularly environmental chemistry) than can national-level assessments that require generalization across multiple ecoregions. Therefore, it is recommended that, when appropriate, regional- or national-level ecological risk assessments be subdivided into metal-related ecoregions, referred to as *metalloregions* (McLaughlin and Smolders, 2001), such that protection levels, mitigation goals, and ranking results will be appropriate for the suite of species naturally present within each type of controlling environment. This is directly analogous to the use of ecoregions when establishing water quality criteria (Griffith et al., 1999). The Problem Formulation phase of the assessment should clearly identify whether a regional approach is being used and, if so, how the metalloregions are defined in terms of species composition and environmental controlling factors.

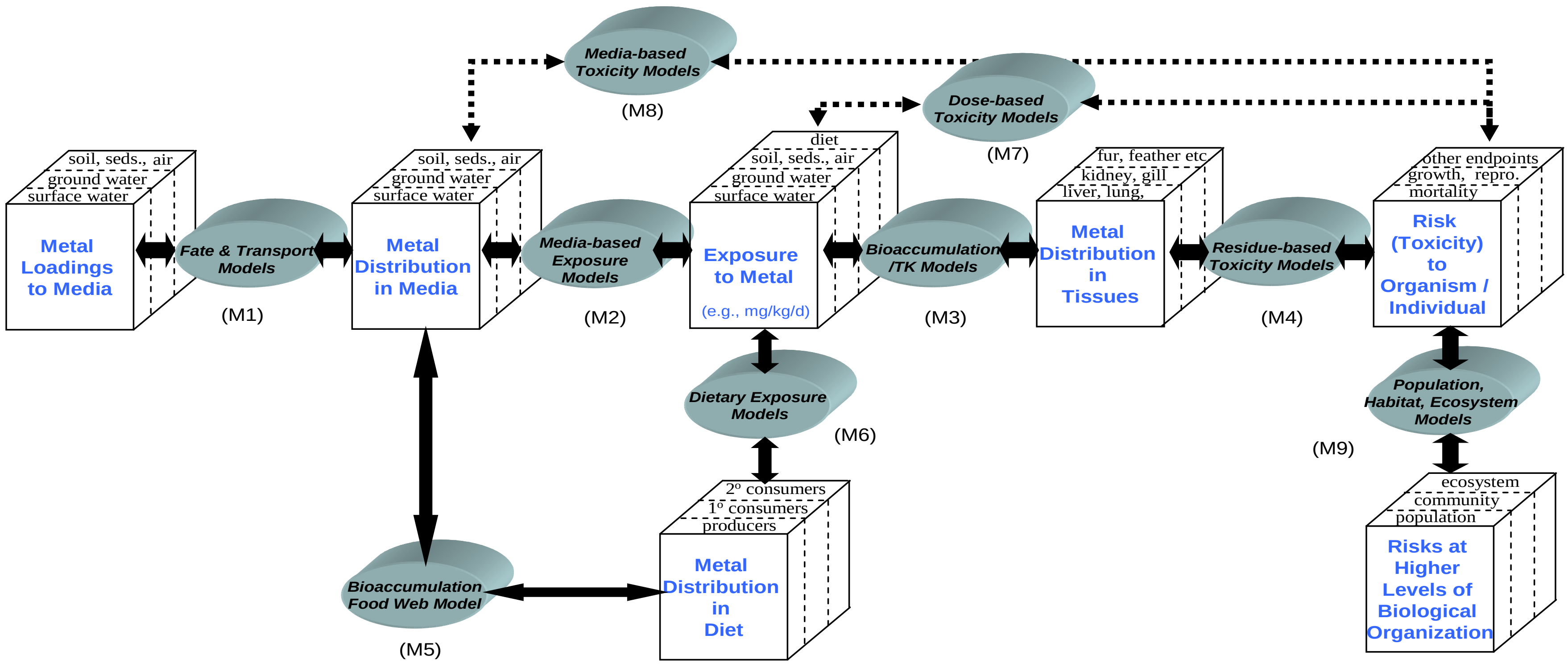

Figure 2-2. Generic conceptual model for metals risk assessment.

This concept of regional-based ecological assessments is significantly less important in *human health* assessments. In these assessments, the environmental controlling factors (pH, water hardness, etc.) may be important determinants in exposure calculations for dietary or drinking water exposures. However, **to our knowledge**, humans have not adapted to particular areas of metal enrichment or impoverishment but, rather, choose to live in all environments. Therefore, the differences in human sensitivity that should be considered are not geospatially correlated. Rather, the assessor should strive to identify potentially sensitive subpopulations, such as the very young or the elderly, subpopulations with genetic predispositions to metal sensitivity (e.g., Wilson's disease), or other similar groups. Again, the scope of the Problem Formulation phase should clearly address whether the risk results will be applied on a population-wide basis, such that protection is afforded to the most sensitive individuals, or whether these groups will be given additional scrutiny and separate risk analyses, such that results will be applicable only to the general population.

Figure 2-2 identifies areas in the conceptual model that stand out as metal-specific issues as the transitions between environmental loadings, media concentrations, exposure receptors, and the final organismal or ecosystem risk. Because metals are naturally-occurring substances with which organisms have evolved, it is particularly important to incorporate the natural processes that affect metal mobility, speciation, biogeochemical cycling, and sequestration into the health risk assessment. These may differ in details or approach, depending on the environment of concern (water, land, and air), the final receptor organisms (humans, animals, and plants), and the management goal (i.e., whether the management goal is the health of individuals or the maintenance of populations or communities). However, the same basic concepts always arise, regardless of the assessment context.

The conceptual model identifies the following issues, indicates the point within the health risk assessment process where they occur, and helps direct the remainder of the health risk assessment.

- **M1: Fate and transport models.** The partitioning and biogeochemical cycling of metals into the various environmental media from the loading source depend on the physical properties of the initial form of the material and the particular chemistry of the receiving environment. Fate and transport models are useful for estimating metal speciation, transition kinetics, partitioning, deposition, and potential resuspension within the context of environmental levels of the metal and other inorganic substances. These can be very detailed for site-specific assessments, or they can provide a potential range of processes that might occur over large, regional scales for assessments of a more generic nature (e.g., criteria development or ranking schemes). Reviews by Paquin et al. (2003), Allen (2002), and EPA (1997a) include up-to-date information with regard to the availability of models appropriate for use in evaluating fate and transport of metals in aquatic environments (see Chapter 3 on environmental chemistry).

- **M2: Media-based exposure models.** Media-specific exposure models are mathematical functions used to calculate the exposure of the organism to metals directly from abiotic media (i.e., excluding the food web). Estimating the uptake of metals from environmental media into biota follows many of the same processes used for organic substances, such as understanding dietary preferences, ingestion rates, inhalation rates, and movement patterns. Of particular concern with metals health risk assessments is accounting for the differing bioavailability of metal species to organisms from different environmental media. Exposure to existing environmental levels of metals is another issue of considerable importance in this modeling step. Exposure assessment issues are considered separately for human health, aquatic, and terrestrial receptors (see Chapters 3, 4, and 5, respectively).

- **M3: Bioaccumulation and toxicokinetic (TK) models.** Many organic substances require metabolic activation to become toxic or, conversely, to be detoxified and excreted. Metals do not. Metals may form complexes with proteins or other carrier molecules for distribution to target organs or for sequestration and excretion. Their bioaccumulation is tissue-specific (e.g., cadmium [Cd] in kidneys). The natural occurrence of metals has led to the development of specific mechanisms for uptake, metabolism, distribution/storage, and excretion of metals by organisms. These processes can impact the use and interpretation of bioaccumulation data and the toxicity of bioaccumulated metal.

- **M4: Residue-based toxicity models.** If risk to the organism(s) of concern is to be based on an estimate of internal dose, then information about the relationship of whole-body (or target organ) residue levels to toxic responses should be reviewed by the assessor, either from empirical data or physiologically based toxicokinetic (PBTK) models. Because of the processes discussed in the previous paragraph, this can be particularly challenging for inorganic metals. Metal speciation in the exposure matrix can especially influence this relationship because uptake and organ distribution kinetics are likely to differ. When available, critical body residues (CBRs) can be used to reduce uncertainties in health risk assessments because they account for site-specific bioavailability and multiple exposure pathways. However, CBRs for metals can vary widely depending on exposure pathway (food vs. water), rate of accumulation relative to the detoxification and sequestration processes, and form of bioaccumulated metal. Establishment of a valid residue-response relationship is critical for successful application of CBRs (see Sections 5.3 and 6.3).

- **M5: Bioaccumulation/food web model.** Movement of metals through the food web is complicated by factors of bioaccessibility, bioavailability, essentiality, regulation of metals (uptake and internal distribution), detoxification, and storage as well as accumulation and the natural adaptive capacity of organisms. While the ability to quantitatively address all these factors may be limited at present, the assessor should at least qualitatively address the potential impacts. Bioaccumulation and trophic transfer of metals does occur. However, biomagnification (i.e., increases in concentration through multiple levels of the food web) is rare, with the exception of certain organometallic compounds, such as methyl mercury, that can biomagnify many orders of magnitude in the aquatic food chain. Discussions of methods for estimating bioaccumulation in aquatic and terrestrial food webs are found in Sections 5.2.5.3 and 6.2.5.2, respectively.

- **M6: Dietary exposure models.** The assessor must carefully consider the bioavailability of metals from food items in models that estimate dietary exposure to metals. In ecological risk assessments, the wide variation in feeding modes and digestive physiology across species limits the ability to make generalizations with metals. Generalizations require knowledge of dietary preferences, trophic structure of the community, and ingestion and absorption rates. In human health risk assessments, the assessor should consider regional, social, and religious dietary preferences. Although this node of the conceptual model differs very little from risk assessment approaches for organic substances, some metal-specific generalities about the relative importance of exposure pathways can be applied to focus (and simplify) the process. For example, the highest accumulation of metals in plants generally occurs in the roots, and, except for hyperaccumulator species, most plant trophic transfer rates can be assumed to be <1. Therefore, direct toxicity to herbivores is less likely than for insectivores or from other dietary pathways, and risk to humans from most fruits and vegetables (except roots or green, leafy vegetables) is low. On the other hand, plants are quite sensitive to some metals and may die before achieving levels high enough to be toxic to animals, thereby affecting them indirectly through reduction in food availability. A discussion of dietary exposure assessment issues is found in Sections 5.2 and 6.2 for aquatic and terrestrial ecological receptors, respectively, and in Section 4.2.5.2 for humans.

- **M7: Exposure-based toxicity model.** Calculation of an external dose (oral intake, gill binding, etc.) for comparison with toxicity thresholds may depend on information about relative bioavailability (RBA), speciation of the metal or metal salt, dietary preferences and rates, environmental concentrations, essentiality, and metal interactions. Toxicity threshold considerations should be based on comparable information, such as appropriate metal species in exposure media, similarly acclimated or adapted organisms, similar exposure routes, and appropriate combinations of essential metals. Chemical equilibrium models such as MINTEQA2 (Brown and Allison, 1987) may be useful for characterizing the species of metal that is present in particular media, making exposure and effect comparisons more comparable. This forms the basis of the biotic ligand model (BLM) approach (Di Toro et al., 2001; Santore et al., 2001; Paquin et al., 1999) to defining acute aquatic toxicity.

- **M8: Media-based toxicity model.** This health risk assessment model compares environmental concentrations with organism response functions without calculating a body burden or internal dose. It is used more frequently for aquatic and soil-dwelling organisms, less frequently for wildlife, and very infrequently for human health assessments. Consideration of RBA, trophic transfer rates, dietary preferences, existing environmental concentrations, and organism adaptations is important for a metals assessment.

- **M9: Population, habitat, ecosystem models.** Assessors who carry out Ecological risk assessments often ask questions related to population growth, habitat change, or ecosystem functions in addition to questions related to risks to individual organisms. Most of the models and approaches are similar for both metal and organic substances. However, metals and other inorganic substances are among the fundamental determinants and delimiters of ecoregions (in conjunction with climate, elevation, and day length associated with latitude). Therefore, knowledge of background levels and the adaptation of organisms to differing metal levels are essential in developing appropriate risk factors for naturally occurring species.

In summary, the conceptual model lays out a series of working hypotheses about how the metal(s) of concern might move through the environment to cause adverse effects in humans or ecological systems. These hypotheses are examined through data analyses, models, or other predictive tools to determine the probability and magnitude of the occurrence of unwanted effects. The approaches used to accomplish this assessement are discussed in general within various Agency risk assessment guidance documents.

2.3. ASSESSMENT PHASE

The assessment phase of a health risk assessment is the process of estimating exposure and understanding the dose-response relationship between biota and the chemical(s) of interest. The additional metals-specific factors should be considered during this phase. As with any assessment, at the beginning of the Analysis phase, the assessor should critically examine the data and models to ensure that they are appropriate to the level of detail and site-specific, regional, or national application of the assessment results. Most of the assessment questions in this chapter are directed toward assisting the assessor with the collection of the appropriate information to address metal-specific issues for conducting either exposure or effects characterizations.

2.3.1. Bioavailability

The bioavailability of metals and, consequently, the associated risk vary widely according to the physical, chemical, and biological conditions under which an organism is exposed. To the extent that available data and methods allow, the assessor should explicitly incorporate factors that influence the bioavailability of a metal into the health risk assessment. In situations where data or models are insufficient to address bioavailability rigorously, the assumptions made regarding

Bioaccessibility, Bioavailability, and Bioaccumulation

Bioaccessibility refers to the amount of *environmentally available metal* that actually interacts with the organism's contact surface (e.g., membrane) and is potentially available for absorption (or adsorption if bioactive upon contact). *Environmentally available metal* is the total amount of metal that is available for physical, chemical, and biological modifying influences (e.g., fate and transport) and is not sequestered in an environmental matrix.

Bioavailability of metals is the extent to which bioaccessible metals absorb onto, or into, and across biological membranes of organisms, expressed as a fraction of the total amount of metal the organism is proximately exposed to (at the sorption surface) during a given time and under defined conditions.

Bioaccumulation of metals is the net accumulation of a metal in the tissue of interest or the whole organism that results from *all environmental exposure media*, 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 (SAB, 2006).

Bioconcentration is the net accumulation of metal in an organism resulting from direct uptake from water only, such as through gill membranes or other external surfaces.

bioavailability should be clearly detailed in the health risk assessment as should the associated impact on results.

Although bioavailability may be a defined measurement when considered in certain vertebrate animals where metal uptake is directly a function of the concentration of metal in the diet, it is not as simple in many other aquatic and terrestrial organisms where food consumption is difficult to measure and where metals are present in the surrounding environment and available for uptake via nondietary pathways. In this case, as discussed in Meyer (2002), metal bioavailability may be more of a conceptual term and not a precisely measured parameter.

Environmental availability refers to the ability of a metal to interact with other environmental matrices and undergo various fate and transport processes. Environmentally available metal is not sequestered in an environmental matrix, and it represents the total pool of metal in a system that is *potentially* bioavailable at a particular time and under a particular set of environmental conditions (i.e., able to contact or enter into an organism). Environmental availability is specific to the existing environmental conditions and is a dynamic property, changing with environmental conditions. The *bioaccessible fraction* of metal is the portion (fraction or percentage) of environmentally available metal that actually interacts at the organism's contact surface and is potentially available for absorption or adsorption (if bioactive upon contact) by the organism.

The bioaccessibility, bioavailability, and bioaccumulation properties of inorganic metals in soil, sediments, and aquatic systems are interrelated and abiotic (e.g., organic carbon) and biotic (e.g., uptake and metabolism). Modifying factors determine the amount of an inorganic metal that interacts at biological surfaces (e.g., human digestive system, at the gill, gut, or root tip epithelium) and that binds to and is absorbed across these membranes. A major challenge is to consistently and accurately measure quantitative differences in bioavailability between multiple forms of inorganic metals in the environment.

The bioavailability issue paper authors (McGeer et al., 2004) provided EPA with some practical, standard, and defensible recommendations on concepts, terms, and definitions that can serve as a paradigm for studying inorganic metals and their bioavailability. Figure 2-3 presents a conceptual framework along with further discussion of metals bioavailability and bioaccumulation.

2.3.2. Exposure Characterization

Exposure characterization describes potential or actual contact or co-occurrence of stressors with receptors (U.S. EPA, 1998a). Metal factors incorporated into this portion of the health risk assessment include ecosystem and receptor characteristics that affect the movement of metals in the environment including atmospheric deposition, their uptake and accumulation in humans and other biota, and distribution into target organs. Specific assessment questions include the following:

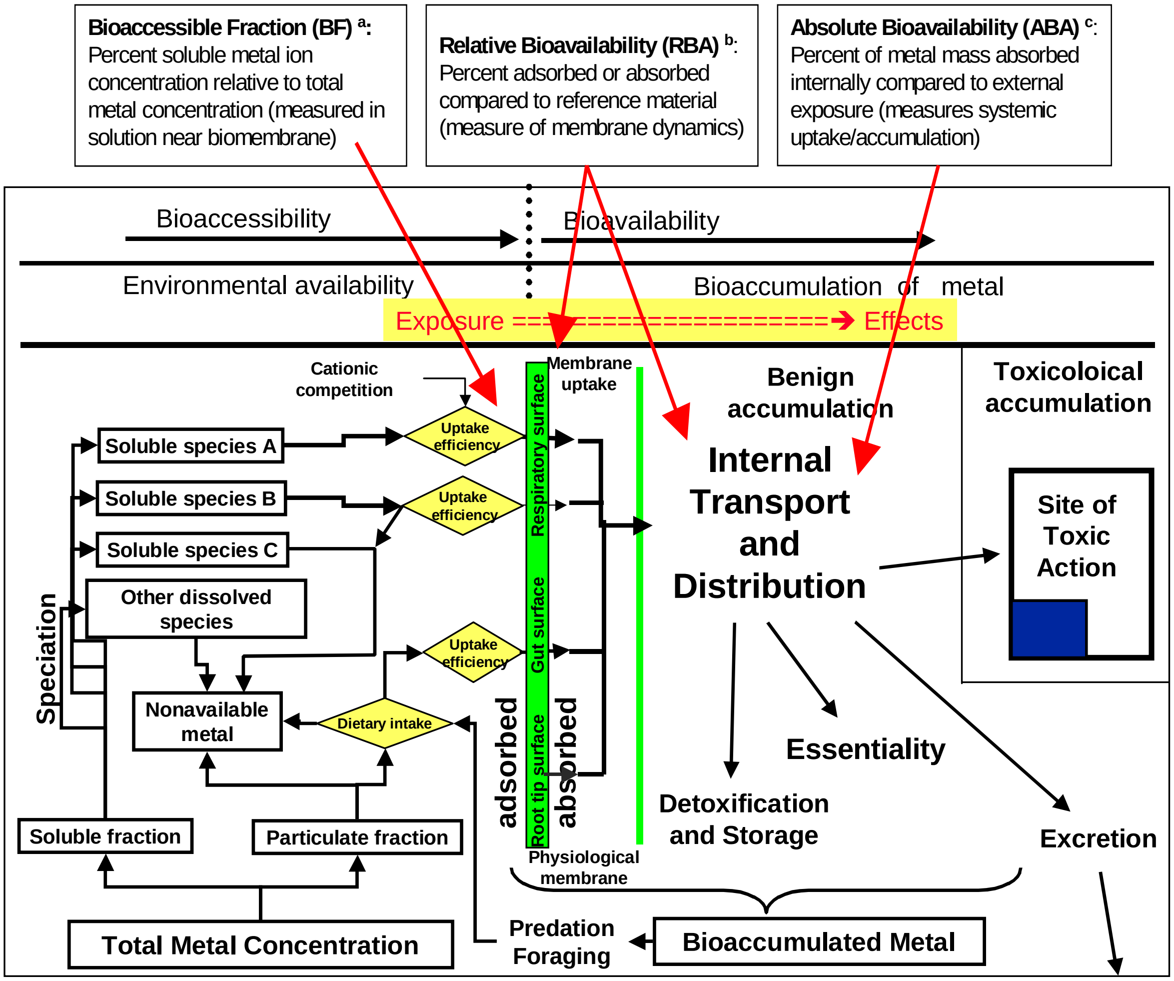

Figure 2-3. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems.

[a]BF is most often measured using *in vitro* methods (e.g., artificial stomach), but it should be validated by *in vivo* methods.
[b]RBA is most often estimated as the relative absorption factor, compared to a reference metal salt (usually calculated on the basis of dose and often used for human risk, but it can be based on concentrations).
[c]ABA is more difficult to measure and used less in human risk; it is often used in ecological risk when estimating bioaccumulation or trophic transfer.

Source: McGeer et al. (2004).

Background Concentrations

- What data sources are used to estimate background (natural and anthropogenic) concentrations?
- What are the ranges of background concentrations and how do they vary spatially?
- What degree of certainty exists in estimates of background concentrations?

Fate and Transport

- What environmental transport and air deposition models will be used and what are their assumptions, limitations, and uncertainties?
- How will the environmental chemistry (in air, water, and soils) of metals be addressed?
- What deposition scale (local, regional, or national) is important for the metal and receptors being considered?
- What meteorological factors impacting the fate and transport of metals should be considered in the health risk assessment?

Mixtures and Interactions

- Is exposure to metal mixtures being incorporated into the exposure assessment? If so, how is it being addressed? If not, what is the rationale for not addressing metal mixtures?
- What evidence exists to indicate exposure to the metal(s) of concern is affected by metal mixtures in the assessment?

Essentiality

- For essential metals, will exposure concentrations exceed the nutritional requirements (recommended dietary allowance [RDA])?
- How do the nutritional requirements vary across species and populations in the assessment?

Forms of Metals

- What forms (chemical species) of metals are likely to occur at the site(s) of interest?
- What biogeochemical speciation and transformation processes are relevant for the assessment?
- How might these biogeochemical processes impact exposure assessment for the metal(s) of concern?

- What transport and fate models are relevant for the environment and metals of concern?

Toxicokinetics/Toxicodynamics of Metals

- What environmental factors have the most influence on the bioavailability of the metals of concern?
- What methods will be used to address bioavailability in the assessment?
- How is bioaccumulation being assessed or predicted?
- To what extent are bioaccumulation predictions being extrapolated across species, exposure concentrations, locations, or environmental conditions?
- What are the key assumptions being used to address bioaccumulation and bioavailability and how accurate are these assumptions?

The objective is to produce a complete picture of how, when, and where exposure occurs or has occurred by evaluating sources and releases, the distribution of the stressor in the environment, and the extent and pattern of contact or co-occurrence with humans or ecologically relevant biota. The metal-specific exposure factors discussed in this framework contribute to the exposure characterization, but additional issues that are generally applied to all health risk assessments also should be considered (although they are not specifically discussed here). For the exposure profile to be useful, it should be comparable with the stressor-response relationship generated in the effects characterization.

2.3.3. Characterization of Effects/Hazard Analysis

To characterize effects or adverse responses to metals, the risk assessor should describe how the effects are elicited, link them to the human populations at greatest risk and/or the ecological assessment endpoints, and evaluate how they change with varying exposure levels. It is particularly important, especially for inorganic metals, to confirm that the conditions under which the exposure occurs are consistent with those of the conceptual model. This will ensure that the correct metal species is evaluated for its effects on the populations (including the vulnerable subpopulation) or endpoints of concern, or that appropriate models are used for extrapolating responses among metal species, biota (laboratory to field, or test species to humans), or for varying environments (e.g., metalloregions). Assessment questions regarding metal-specific factors for effects analyses or hazard assessments include the following:

Background Concentrations

- What is the relationship between environmental (natural and anthropogenic) concentrations and toxicologically relevant metal concentrations?

- For ecological risk assessments, how are acclimation, adaptation, and tolerance issues being addressed in the effects analysis?

- In human health assessments, have concentrations in locally grown or harvested foods been taken into account when estimating elevated metal exposures or estimating relative bioavailability of metals in foods, soil, or water?

- How representative are the toxicity test conditions of the environments being assessed?

Mixtures and Interactions

- Are toxicological effects of metal mixtures being incorporated in the effects assessment? If so, how are they being addressed? If not, what is the rationale for not addressing the toxicity of metal mixtures?

- For particular mixtures of inorganic metals, to what degree are their combined effects additive, antagonistic, or synergistic?

- Is mimicry (competitive interactions among chemically similar metals/metalloids) important in the assessment?

- For site-specific assessments, what evidence exists to indicate the toxicity of the metal(s) of concern is affected by the presence of other metals?

Essentiality

- For essential metals, are nutritional requirements known (e.g., RDA for humans)?

- What is the range between concentrations required nutritionally and those associated with toxicity reference values (e.g., reference concentration [RfC], Ambient Water Quality Criteria [AWQC]) or adverse effect levels used in the risk assessment?

- Are nutritional deficits that can increase the vulnerability of humans and other organisms to other stressors being addressed?

Forms of Metals

- Which forms of the metals are most toxicologically relevant?

- How toxicologically comparable are the forms of metals used in the effects and exposure assessment?

- How might assumptions regarding the toxicity of different metal forms impact the effects assessment? How accurate are these assumptions?

- How will the atmospheric chemistry, transport, and deposition of metals be addressed in the assessment?

- What meteorological factors impact the fate and transport of metals?

Toxicokinetics/Toxicodynamics of Metals

- How does toxicity vary for different metal forms found (or likely to be found) in the assessment?

- Which of these are most important and which are incorporated into the effects assessment?

- How are absorption, distribution, metabolism, and excretion addressed for individual metals or mixtures of concern?

Effects analysis results are summarized in a stressor-response profile. The analysis addresses the plausibility that effects may occur or are occurring as a result of exposure to the metal(s) of concern, and that linkages between measured effects and assessment endpoints can be made (this is especially important for ecological risk assessments). Many of these steps in effects assessments are not unique to inorganic metals, and so they are not addressed specifically in this Framework.

Although the prediction of toxicity due to dietary exposure to inorganic metals is complicated by wide variation in the bioavailability and toxicity of metals, it is a factor that risk assessors should consider in metals assessments. Direct approaches to accomplish this include quantifying the bioavailable fraction of bioaccumulated metals in consumers (e.g., analysis of tissue fractions such as cytosolic metals) and determining metal speciation in the media of concern (water, soil, or air). Comparisons of media values can then be made to toxicity reference values using the same metal species. Lacking such information, or for higher tier assessments, bioassay methods with field-collected media offer another way to assess bioavailability, although other than lead exposure in juvenile swine, such methods have not been widely standardized.

2.4. RISK CHARACTERIZATION

Risk Characterization is the final phase of the health risk assessment and is the culmination of the Planning, Problem Formulation, and Analysis of predicted or observed adverse effects. It combines the results of the exposure assessment with information on stressor-response profiles to estimate the likelihood of effects of specified magnitude(s). The risk assessor should describe available lines of evidence and conduct (and report) an uncertainty analysis. Conclusions presented in the Risk Characterization should provide clear information to risk managers that is useful for decision making. There are no metal-specific methods in the

Risk Characterization, other than revisiting the metal factors described above to verify that they were accorded proper consideration during the Analysis. However, because metal assessments are dependent on specific attributes of environmental chemistry and biological responses related to the natural occurrence of metals, it is particularly important that the Risk Characterization specify the conditions, locations, and time-frame within which the assessment results are applicable.

For risk assessments conducted for regional or national assessments, criteria development, or ranking purposes, it should be acknowledged that results will be based on organisms and soil types that result in greatest bioavailability and sensitivity. Care should be taken, however, that the organism-environment combinations assessed are, in fact, compatible with real-world conditions. Relevant assessment questions include the following:

Background Concentrations

- What assumptions are made regarding background (natural and anthropogenic) concentrations in characterizing metal risks?
- How sensitive are the risk assessment results to the presence of background concentrations (i.e., are background concentrations a major or minor component of the risk estimate)?
- Have metals with generally high background concentrations (e.g., aluminum (Al) and iron (Fe) in soil) been appropriately considered in ecological assessments?

Mixtures and Interactions

- How sensitive are the risk assessment results to assumptions regarding exposure and effects of metal mixtures?
- To what extent do the methods and assumptions regarding the exposure and effects of metal mixtures introduce intentional or unintentional bias in the Risk Characterization?

Essentiality

- How do risk assessment results compare to levels required to maintain nutritional health?
- How sensitive are the risk assessment results to methods and assumptions used to address essentiality?
- To what extent do the methods and assumptions regarding the exposure and effects of essential metals introduce intentional or unintentional bias in the Risk Characterization?

Forms of Metals

- How sensitive are the risk assessment results to methods and assumptions used to address the different metal forms?

- To what extent do the methods and assumptions regarding the exposure and effects of metal forms introduce intentional or unintentional bias in the risk assessment?

Toxicokinetics/Toxicodynamics of Metals

- How sensitive are the risk assessment results to methods and assumptions regarding factors affecting bioavailability and bioaccumulation of the metal?

- To what extent do the methods and assumptions regarding the factors affecting bioavailability and bioaccumulation of metals introduce intentional or unintentional bias in the risk assessment?