2. PROBLEM FORMULATION AND METALS PRINCIPLES

The risk assessment phase of identifying important issues and outlining the scope of both human health and ecological risk assessments is commonly referred to as "problem formulation" (U.S. EPA, 2003a, 2000a, 1998a). Metals have a number of characteristics that require special consideration early and throughout the risk assessment process. This chapter states the major principles underlying metals analyses and provides guidance on how to set up the conceptual model and scope of the assessment to account for metals-specific differences in risk analysis.

Metals are naturally occurring constituents of the environment. Consequently, biota have evolved and continue to evolve in their presence. Thus, naturally occurring levels of metals play an important role in the biogeographic distributions of plants and animals and may, in fact, be limiting factors in species distributions or landscape uses. Therefore, during the problem formulation phase of an assessment of anthropogenically elevated metals, it is important to clearly define the geospatial area to which the results will apply and to identify environmental controlling factors (e.g., pH, organic matter, iron, aluminum) and the resulting naturally occurring differences in biota composition and metal sensitivity (see Section 4.1, Environmental Chemistry).

For metals, the type of assessment (i.e., screening or definitive) 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, natural background concentrations, and species sensitivities. For regional and national-scale assessments, more general assumptions about the form of the metal in the environment, uptake and bioavailability parameters, and sensitive species or subpopulations are useful, frequently producing results that are conservative in their assumptions in order to be protective of sensitive species or locations. Regardless, the fundamental principles that determine the form of metal in the environment and, consequently, the transport of metals through environmental media to accumulate or cause toxic responses in biota should be considered in all risk assessments.

2.1. PRINCIPLES OF METALS RISK ASSESSMENT

One of the purposes of this document is to present key principles that contain issues or processes that differentiate inorganic metal compounds from other chemicals when assessing their risk to human health and the environment. While we recognize that organic compounds, for example, undergo bioaccumulation, there are unique properties, issues, and processes within these principles that assessors should consider when evaluating metal compounds. Contributors to the Metals Action Plan (MAP), members of the Science Advisory Board, and external stakeholders, along with various contributers to and authors of the framework, have discussed these metals principles for consideration in the assessment of metals. The following discussion of topics under each of these principles reflects this extensive deliberation and describes unique aspects of inorganic metal compounds that should be considered when risk assessments are conducted. The principles focus on unique properties of inorganic metal compounds, and this chapter discusses why these principles are important for risk assessments. These principles should be addressed and incorporated into metals risk assessments to the extent practicable. They are visible throughout this document. In Chapter 3, they are expanded upon with recommendations to guide assessors, and in Chapter 4, specific topics are discussed in more detail.

Metals Principles

Environmental background concentrations
Essentiality
Environmental chemistry
Bioavailability
Bioaccumulation and bioconcentration
Acclimation, adaptation, and tolerance
Toxicity testing
Mixtures

2.1.1. Environmental Background Concentrations

Because metals are naturally present in the environment, it is important to consider the background concentrations of metals when conducting risk assessments. How to incorporate this unique aspect of metals in risk assessments is a common challenge. The following key questions arise:

- *How should the cumulative exposure and risk of background and anthropogenic or "added metal" be considered in risk assessments?*

- *How do the natural background levels of metals influence the types of ecological receptors that are naturally present and appropriate to consider in risk assessments?*

Only the bioavailable fraction of background concentrations contributes to total metal exposure and overall risk. Test organisms should be acclimated to background conditions, and appropriately adapted organisms should be used for site-specific assessments.

Background should be defined in a specific spatial and temporal aspect related to the scope of the particular hazard or risk assessment. Background metal concentrations can vary by as much as five orders of magnitude, depending on soil type, geography, and other factors (Chapman and Wang, 2000). Background may exacerbate toxicological effects and accumulations of metals from direct emissions or other regulated sources or, conversely, it may result in adaptation of organisms to higher metal concentrations and result in increased tolerance to emissions. Furthermore, because metals occur naturally, and some are essential macro- or micronutrients, they are at least partially responsible for how plants and animals are distributed within various ecoregions. The distribution of plants and animals, local species diversity, species survival, and the vitality of individuals can be profoundly affected by background levels of metals in an area. Humans, on the other hand, are distributed throughout the world, irrespective of naturally occurring levels of metals.

Background

Background is defined as the amount of metals occurring in soil, water, air, and biota as a result of anthropogenic and natural processes. Anthropogenic contributions are limited to those that are 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 is not specifically related to the release in question (U.S. EPA, 2003e).

The contribution of the background level of a metal(s) to the cumulative exposure of people and other organisms may be significant and so should be considered in any human health assessment (see Section 4.2.2.1). Lifestyle choices expose people to metals in many different contexts that warrant consideration when assessing the added risk caused by a particular source. However, the added risk from dietary or other point sources should be considered in light of the relative bioavailability of the background and additional sources. Background metals generally are reduced in bioavailability as a result of aging in soils or sediments (see Section 4.1.6.4) or transformation to less bioavailable salts.

2.1.2. Essentiality

Some metals are essential to maintaining proper organism health and may cause adverse effects when present at deficient or excess amounts. The influence of metals essentiality on exposure and effects of the metal(s) of concern should be addressed to the extent practicable in the assessment.

As a practical matter, essentiality sets a lower bound on the range of metal exposures to be considered with respect to the potential for toxic effects. The following discussion highlights the issue of essentiality; further discussion is found in Sections 4.3.2 and 4.5.1. Seven metals are known to be nutritionally essential for humans, and four others have been shown to have possible beneficial effects (Table 2-1); these are reviewed in detail in Goyer et al. (2004). Plants and other animals also depend on certain metals (See Table 4-14), and thus the generalizations about essentiality apply for these organisms as well. The list of metals with no known beneficial human health effects is longer, and some examples are given in Table 2-1.

Table 2-1. Classification of selected metals based on characteristics of health effects

Nutritionally essential metals	Metals with possible beneficial effects	Metals with no known beneficial effects
Chromium III Cobalt Copper Iron Manganese (animals but not humans) Molybdenum Selenium Zinc	Arsenic Boron Nickel Silicon Vanadium	Aluminum Antimony Barium Beryllium Cadmium Lead Mercury Silver Strontium Thallium Tin

The response of humans and other organisms to exposure to these metals is conceptualized as having three phases: the Deficiency zone, the Optimal or inactive zone, and the Toxicity or toxicological action zone (Figure 2-1).

2.1.3. Environmental Chemistry

The environmental chemistry of metals strongly influences their fate and effects on human and ecological receptors.

Table 2-2 identifies factors governing the chemistry of metals in sediments, soils, and waters. Metals do not degrade but, rather, transform and exist as multiple interconverting species, the exact mixture of which depends on the environmental chemistry of the medium. Because the behavior of metals differs, it is necessary to understand the chemistry of the particular metal and the environment or medium of concern. Still, some generalizations can be made about factors that control metal chemistry and environmental characteristics. These allow risk assessors to develop preliminary estimates of metal exposure and effects and are discussed in Section 4.1.

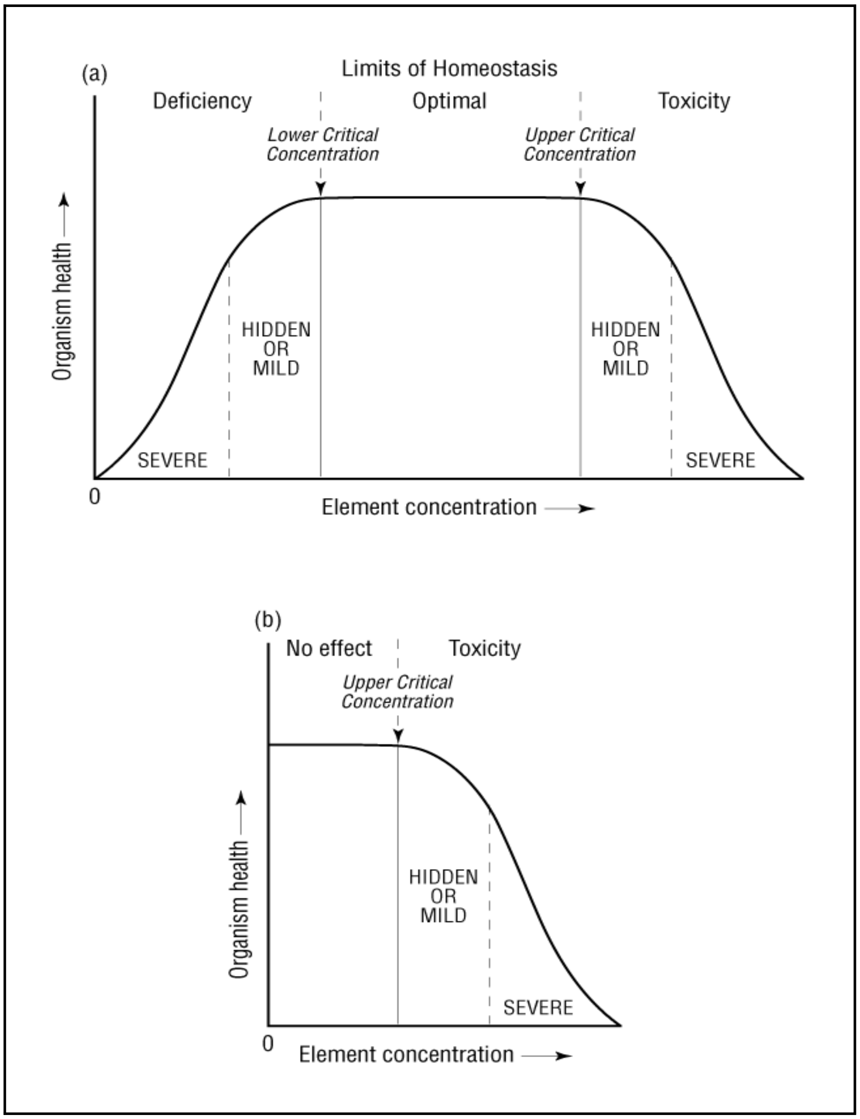

Figure 2-1. Health effect curves for (a) essential elements and (b) nonessential metals.

Source: Fairbrother and Kapustka, 1997.

Table 2-2. Factors that primarily control metal sorption to soils, aquifers, and sediments

Soil solids	Soil solution	Solutes
Soil mineral composition Specific surface areas of metal-sorbing solids Surface site density or cation exchange capacity of metal-sorbing solids Aeration status Microbial type, activity, and population Organic matter content and character Temperature	pH Eh Dissolved oxygen Solute composition Dissolved organic carbon Ionic strength Temperature	Chemical identity Complexation chemistry Solubility Precipitation chemistry Redox behavior Vapor pressure

2.1.4. 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, factors that influence the bioavailability of a metal should be explicitly incorporated into assessments. In situations where data or models are insufficient to address bioavailability rigorously, the assumptions made regarding bioavailability should be clearly articulated in the assessment as should the associated impact on results.

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., 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

Bioavailability, Bioaccessibility, and Bioaccumulation

Bioaccessibility of metals is the portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (e.g., fate, transport, bioaccumulation). It is termed the *environmentally available fraction* and also known as *environmental availability*.

Bioavailability of metals is the extent to which bioaccessible metals adsorb onto or absorb 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 exposure from all environmental sources, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a steady-state balance of losses from tissue and the body.

practical, standard, and defensible recommendations on concepts, terms, and definitions that can serve as a paradigm for studying metals and their bioavailability. A conceptual framework along with further discussion of metals bioavailability and bioaccumulation is presented in Section 4.1 and Figure 2-2.

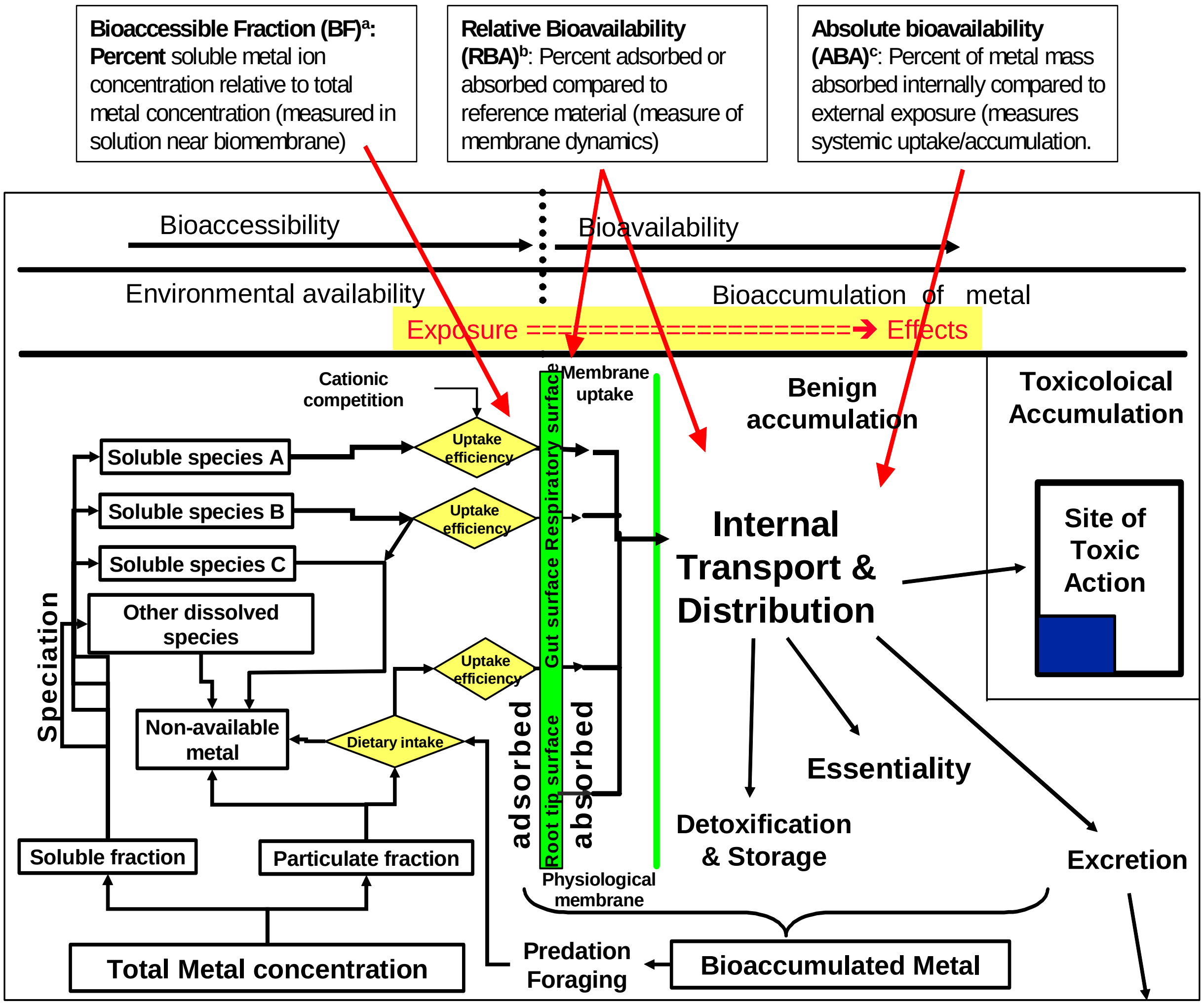

Figure 2-2. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems.

[a]BF is most often measured using *in vitro* methods (e.g., artificial stomach), but 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.

2.1.4.1. *Bioaccessibility or Environmental Availability*

The portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (e.g., fate, transport, bioaccumulation) is termed the *environmentally available fraction*. 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 to (able to contact or enter into) an organism. The *bioaccessible fraction* of metal is the portion (fraction or percentage) of environmentally available metal (e.g., <250 µm diameter for vertebrates) that actually interacts at the organism's contact surface and is potentially available for absorption or adsorption (if bioactive upon contact) by the organism (see Figure 2-2).

Environmental availability refers to the ability of a metal to interact with other environmental matrices and undergo fate and transport processes. Environmental availability is specific to the existing environmental conditions and is a dynamic property, changing with environmental conditions. As an example of environmental availability, the divalent cation of copper (Cu^{2+}) is available for interaction with the gills of a sediment-dwelling invertebrate, binding to dissolved organic matter, and advective transport, whereas copper in the form of a sulfide in sediments is not. Resuspension of sediments with copper sulfide may introduce oxygen and result in the release of divalent copper into the water column, making it environmentally available.

2.1.4.2. *Bioavailability*

The concept of metal bioavailability includes metal species that are bioaccessible and are absorbed or adsorbed (if bioactive upon contact) by an organism, with the potential for distribution, metabolism, elimination, and bioaccumulation. Metal bioavailability is specific to the metal salt and particulate size, the receptor and its specific pathophysiological characteristics, the route of entry, duration and frequency of exposure, dose, and the exposure matrix. To date, for most metals, the treatment of bioavailability for human health assessments is to assume that the bioavailability of the metal exposure from the site is the same as the bioavailability derived from the toxicity study that has been used to derive the toxicity value (Reference Dose or Cancer Slope Factor).

2.1.4.3. *National Research Council Report*

The National Academy of Science (NAS), National Research Council (NRC) report on bioavailability of contaminants in soils and sediments provides a broad overview of chemical availability issues in environmental media and within biota (NAS/NRC, 2002). As illustrated in Table 1-1 of the NRC document, many variations of terms and definitions are used for the concept of "bioavailability." The NRC report reviews the history and nuances of the various terms and meanings involving "bioavailability processes." The metals framework responds to the NRC report's recommendations on making bioavailability processes visible in risk assessments and improving the scientific basis supporting bioavailability in risk assessments. It sets forth principles and tools that are responsive to the NRC recommendations, although the NRC report lists additional tools, with their strengths and limitations, that also may be applicable to evaluating bioavailability. Although the NRC report states a preference for mechanistic approaches, decisions also may be made using assumption and degrees of uncertainty, particularly for national-scale assessments and ranking.

2.1.5. Bioaccumulation and Bioconcentration

Organisms bioaccumulate metals through multiple mechanisms of uptake, distribution, metabolism, and elimination. The highly complicated and specific nature of metals bioaccumulation substantially hinders the ability to accurately predict bioaccumulation and extrapolate results across species and exposure conditions, particularly when simplified models are used (e.g., Bioaccumulation Factor, Bioconcentration Factor).

Because plants and animals have evolved in the presence of metals, some of which are required for proper physiological functioning, they have developed a variety of physiological and anatomical means to regulate the amount of metals in their tissues. For some metals, this includes storage in various compartments (e.g., lead in bone or cadmium in kidney). Such bioaccumulation of metals may cause no effects or may eventually result in a toxic response. Should the organism be eaten by another (e.g., an herbivore eating a plant that has stored metal in its foliage or a predator eating a mollusc that has accumulated metal granules), the stored metal may (or may not) result in toxicity to the consumer, depending on the form in which it was stored. Therefore, the mere presence of a metal in an animal or plant cannot always be used to infer toxicity to either the organism itself or to its consumers. If the concentration of metal in an organism is greater than the environmental media (soil, water, or sediment), then the metal is said to *bioconcentrate*. If the organism's metal burden is from *both* environmental media and food intake, then the metal is said to *bioaccumulate*. *Biomagnification* occurs in the food web if each trophic level has a higher amount of metal than the one below it. This occurs readily for persistent organic substances that are highly lipophilic, but generally it is not the case for metals. Organisms at all trophic levels have developed mechanisms to regulate internal metal concentrations and generally exhibit toxic effects and die before tissue levels become very high. Exceptions are organometallic compounds such as methyl mercury or organoselenium and the specialized metal hyperaccumulating plants that use metal storage as a means of detoxifying their environment or discouraging feeding by consumer organisms.

2.1.6. Acclimation, Adaptation, and Tolerance

Metals naturally occur at a range of environmental concentrations and are influenced by local biogeochemical controls on metal cycling. Within limits, organisms have developed mechanisms for coping with excess metals exposure (e.g., acclimation, adaptation).

Organisms have developed various mechanisms to cope with variable background metal concentrations through either active or passive uptake and elimination processes. Additionally, organisms can acclimate to suboptimal metal levels by changing various physiological functions, and populations can undergo genetic change (adaptation) and develop increased tolerance to different levels (Rusk et al., 2004; Wallace and Srb, 1961). For example, the fact that plants of diverse taxonomic relationships can grow on soils high in metals provides evidence of adaptation for metal tolerance.

Tolerance, Acclimation, and Adaptation

Tolerance is the ability of an organism to maintain homeostasis under a variety of environmental conditions, such as variable metal concentrations.

Acclimation is how an individual develops tolerance during its lifetime, and it may be gained or lost. Acclimation is also called *phenotypic plasticity*.

Adaptation is a genetic change over multiple generations as a response to natural selection. Traits are not lost during single lifetimes. Adaptation is also known as *genotypic plasticity*.

This ability for organisms to tolerate various amounts of naturally occurring metals makes it difficult to generalize about effects levels that are applicable and consistent to all organisms in all habitats. Furthermore, this capacity for change makes it important to acclimate organisms to test conditions when setting up bioassays for toxicity tests. Conversely, results of tests conducted with organisms reared in media with low natural metal levels may not be representative of effects to organisms that normally experience high metal concentrations (or vice versa). This raises difficult questions about general applicability of test data and relevance for site-specific assessments. Concerns about adaptation or acclimation have less relevance for humans, as there are only a few examples of development of metal tolerance among specific populations.

2.1.7. Toxicity Testing

Owing to limitations in available data and test methods, application of laboratory-derived toxicity data often requires extrapolation of results across test species, metal compounds, and exposure conditions that affect bioavailability. Toxicity data should be expressed in a manner comparable to environmental exposure estimates, thus accounting for bioavailability, tolerance (acclimation and/or adaptation), and species-response effects. Toxic thresholds for essential elements should be set at levels higher than required daily intake.

Homeostatic mechanisms regulate the toxic response of an organism to metals. There are a variety of ways, however, in which homeostatic control mechanisms can be overwhelmed or circumvented, resulting in a toxic effect of the metal. Because soluble metal salts are often used in toxicity testing, test experimental designs may need to be adapted to assess more common environmental forms of metals, competition between essential and nonessential metals, and other factors.

2.1.8. Mixtures

Metals frequently occur as mixtures owing to their natural abundance in the environment and the dietary essentiality of some metals for normal physiological functioning. Metals may interact either synergistically, additively, or antagonistically in various ways, depending on the combinations of metals and their relative amounts.

The presence of multiple metals can lead to competition among these metals for the complexation capacity of the water, resulting in a decrease in complexation capacity relative to what would be available for any single metal alone. This has direct implications to the evaluation of metal availability and the potential for adverse effects. Such interactions are most important when considering low-effect levels for the metal of interest, increasing in importance as the concentrations of competing metals increases. Another problem with multiple metals is that toxic interactions could exacerbate effects on the target organism. This could be in the form of a single effect being exacerbated, as would be the case when the two metals have the same mode of action (e.g., copper and silver affecting sodium regulation, or zinc and cadmium affecting calcium regulation), or it could result in an organism being affected in different ways at the same time when the modes of action differ. Metal interaction might also lead to a decrease in the rate of uptake by one at the expense of the other, not only when trace metals such as cadmium, strontium, or zinc interact with a hardness cation such as calcium, but when metals such as lead and copper interact with each other as well.

Metals are normally found in the environment as mixtures with other metals as well as organic compounds. Two key questions should be asked when assessing metals mixtures. First: To what extent does each metal contribute to any observed joint effect? (Recognize that when the relative compositions of metals in the mixture change, this change the answer.) Second: Are the effects significantly greater or lesser than the sum of the individual component effects? Some metals can exert a protective or sparing effect when combined with others, thereby mitigating risk (antagonistic) while others can enhance the toxic effect (synergistic). For example, zinc may mitigate mercury toxicity, and copper may have a protective effect against cadmium poisoning, while copper deficiency can enhance the effects of lead.

2.2. METALS CONCEPTUAL MODEL

The relationships between the sources, exposure, and effects of metals to human and ecological receptors are complex and specific to the site, environmental condition, and receptor organism. Because metals are naturally occurring substances, 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 occurs with xenobiotic organic contaminants. These transition functions should be specifically identified in the conceptual model for all metals assessments.

A conceptual model depicted in Figure 2-3 shows the interrelationship between the metals or metal compounds of interest and the 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 model depicts possible pathways from sources of metals to receptors and includes environmental or biological processes that may influence the predominant route of exposure or the physical/chemical properties of the metal compounds.

The goals and scope of an assessment, in addition to the availability of data, methods, and resources, are among the most important factors that determine the extent to which key metal principles should be incorporated into an assessment. Generally, assessment endpoints are selected during the problem formulation phase of all risk assessments based on their relevance to management goals, societal values and laws, known adverse effects of metals, and endpoints of importance to stakeholders. Risk assessors will incorporate metal principles to a lesser extent in screening level assessments than in definitive 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 risk assessments be subdivided into metal-related ecoregions, known 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.

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, 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, consideration should be given to the identification of potentially sensitive subpopulations, such as the very young or the elderly, those with genetic predispositions to metal sensitivity (e.g., Wilson's disease), or other similar groups (see Section 4.3, Human Health Effects). Again, the problem formulation phase should clearly state 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 are given additional scrutiny and separate risk analyses, such that results will be applicable only to the general population.

Areas in the conceptual model that stand out as metal-specific issues are identified in Figure 2-3 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 into the risk assessment the natural processes that affect metal mobility, speciation, sequestration, and toxicity. These may differ in details or approach, depending on the environment of concern (water, land, air), the final receptor organisms (humans, animals, plants), and whether the management goal is health of individuals or maintenance of populations and communities of organisms. However, the same basic concepts always arise, regardless of the assessment context.

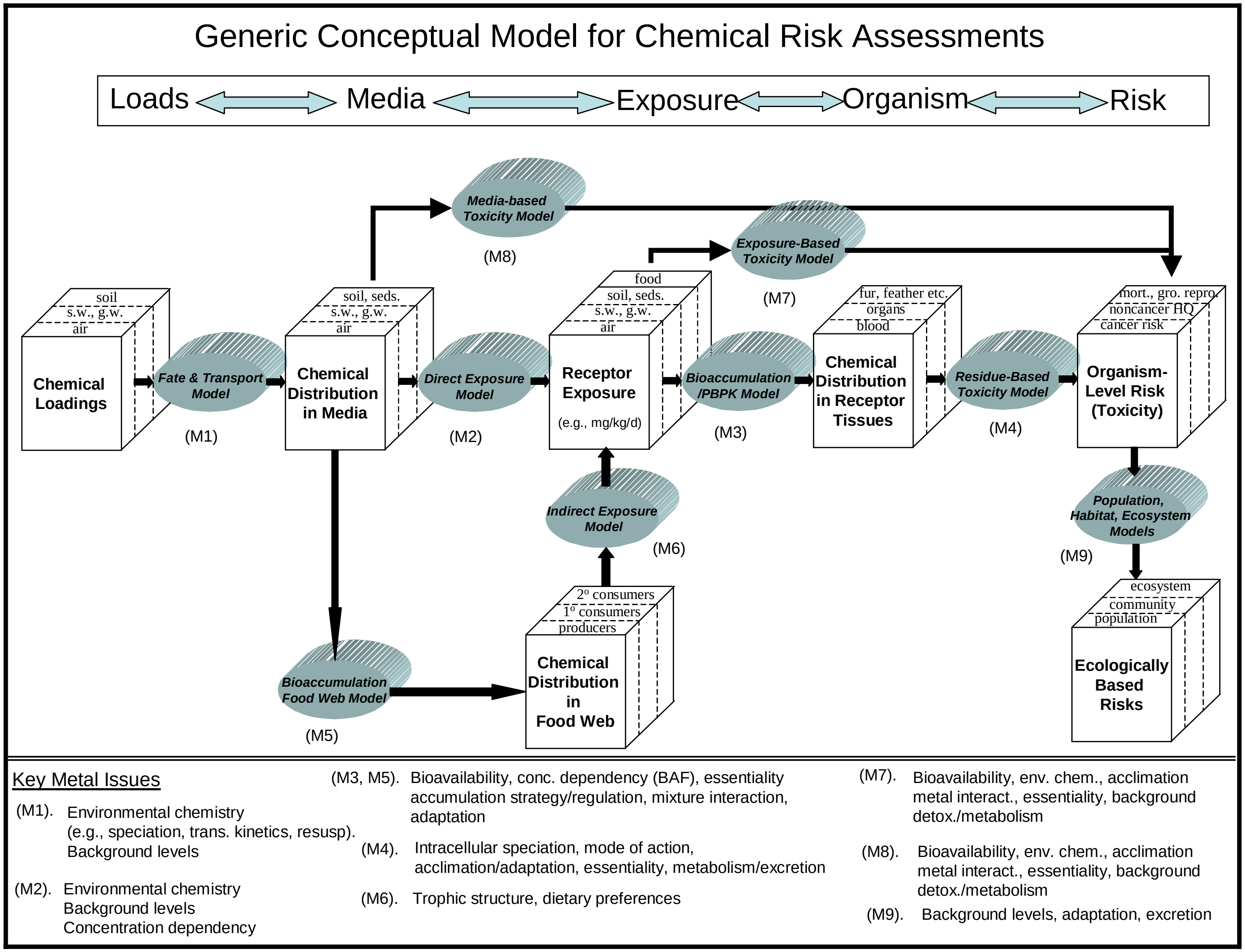

Figure 2-3. Generic conceptual model for metals risk assessment.

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

- **Environmental chemistry (M1).** The partitioning of the metals or metal compounds of concern into the various environmental media from the loading source is dependent on the physical properties of the initial form of the material and the particular chemistry of the receiving environment. Models are useful to estimate speciation, transition kinetics, and potential resuspension of the material within the context of natural background 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). The degree of influence of various environmental attributes on the final distribution of the metals of concern into the various media also can be identified through the application of appropriate models.

- **Exposure models (M2).** Estimating uptake of metals from environmental media into biota follows many of the same processes as for organic substances, such as understanding trophic relationships, dietary preferences, and movement patterns. However, metal-specific issues arise owing to the variable solubility of metal complexes, essentiality of some metals for organismal functions, and naturally evolved processes for uptake, sequestration, or exclusion of these materials.

- **Accumulation and bioaccumulation/physiologically based toxicokinetic (PBTK) and toxicodynamic models (M3).** Although many organic substances require metabolic activation to become toxic or, conversely, to be detoxified and excreted, metals do not. Metals may form a complex with proteins or other carrier molecules for distribution to target organs or for sequestration and excretion. They typically do not bioaccumulate or biomagnify within the whole organism, although they may do so in particular tissues (e.g., lead in bone or cadmium in kidneys). For example, in aquatic systems, the amount of metal taken up in the aquatic environment is proportional to the external concentration (and a function of the internal concentration), so it is not a constant. This is a particularly important distinction between metals and organic substances and is a central aspect to the conceptual approach for assessing risks of metals. It is equally important to understand how different groups of organisms react to metal loading (as accumulators, excluders, or sequesters) to accurately predict potential for immediate or delayed toxicity of metals in the environment. Interactions among metals, particularly for the essential elements, may significantly affect the toxicodynamics of the metal(s) of interest, especially when exposure occurs via complex mixtures of substances. Finally, the near-term experience of organisms with metals (acclimation) or long-term species history (adaptation) can significantly affect how metabolic pathways are adjusted to accommodate higher- or lower-than-normal metals loading.

- **Residue-based toxicity models (M4).** 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 understood, either from empirical data or PBTK/toxicodynamic models. Because of the processes discussed in the previous paragraph, this can be particularly challenging for metals. Metal speciation in the exposure matrix can significantly influence this relationship because uptake and organ distribution kinetics are likely to differ.

- **Accumulation and bioaccumulation/food web model (M5).** This node of a conceptual model applies to ecological risk assessments and, to a lesser extent, human health assessments. Movement of inorganic metals and metal compounds through the food web (or up the dietary pathway for humans) is complicated by factors of bioavailability, essentiality, background concentrations, and natural adaptive capacity of organisms.

- **Indirect exposure model (M6).** The exposure of an organism of concern is dependent on its location within the trophic structure of the community and its 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.

- **Exposure-based toxicity model (M7).** Calculation of appropriate external dose (oral intake, gill binding, etc.) for comparison with toxicity thresholds depends on information about relative bioavailability (RBA), speciation of the metal or metal salt, dietary preferences and rates, natural background 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.

- **Media-based toxicity model (M8).** This 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, natural background concentrations, and organism adaptations is important for a metals assessment.

- **Population, habitat, ecosystem models (M9).** 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, a knowledge of natural background and adaptation of organisms to differing metal levels is 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 analysis, models, or other predictive tools to determine the probability and magnitude of occurrence of unwanted effects. The approaches used to accomplish this are discussed in general within various Agency risk assessment guidance documents.

2.3. NEXT STEPS

Chapter 3 of this framework provides the risk assessor with a tool box in the form of key recommendations and important considerations for undertaking the risk analysis for human health, aquatic, and terrestrial receptors potentially exposed to metals or metal compounds. It includes recommendations for consideration of metals fate and transport, exposure, and effects. The fundamental metals principles, outlined earlier in Section 2.1, that should be considered throughout metals risk assessment are integrated into these recommendations as appropriate. Chapter 4 of the framework expands on the supporting components of the recommendations and provides the risk assessor with a more indepth discussion of the strengths, limitations, and state of the science of the tools and methods available for metals risk assessment. Section 5 of the framework discusses metals research needs.