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FRAMEWORK FOR METALS RISK ASSESSMENT

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

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FOREWORD

Many U.S. Environmental Protection Agency (EPA, or the Agency) programs face decisions on whether and how to regulate metals. These decisions range from setting standards or permitting for environmental releases, to establishing safe levels in different environmental media, to setting priorities for programmatic or voluntary efforts. A basic input to the decision-making process for most EPA programs is an assessment of potential risks posed by a metal or metal compounds to human health and the environment.

The Agency's Science Policy Council (SPC) recognizes that metals present unique issues when assessing risks or categorizing hazardous substances and the added challenge of addressing the complexity of these issues in a consistent manner across the Agency's various programs. The SPC, therefore, tasked an Agency work group to devise a Metals Action Plan (MAP) to establish a process that will ensure a consistent application of scientific principles for assessing risk for metals. The process should be transparent (i.e., articulate assumptions/uncertainties) and have the flexibility to address program-specific issues (Glaze and Thomas, 2002). The MAP included brief descriptions of the Agency's current activities related to metals assessment and identified critical scientific issues that need to be addressed.

The MAP recommended development of a framework for metals risk assessment. The plan stated that the Framework will offer general guidance to EPA programs for considering the various properties of metals, such as environmental chemistry, bioavailability, bioaccumulation, exposure limitations, and toxicity, when assessing their risks to humans or the environment.

Because of the scientific complexity of the metal-specific risk assessment properties, the Agency recognized the need for inclusion of stakeholders and the public in the development of the Framework, as well as involvement of experts throughout the Agency. A stepwise process was initiated, beginning with the MAP and continuing with development and review of this document. Workshops and peer-review activities were conducted at multiple intervals during the production of the Framework to ensure that the science was current and accurate and that it supported program applications. To gain additional information on metals, the Agency contracted for the development of issue papers on important topics in the assessment of metals. The lead authors were external experts; however, EPA and other federal agency scientists served as co-authors on some of the reports. Scientific workshops were held to discuss appropriate approaches for the issue papers, review the final drafts, and comment on the draft Framework

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document. These workshops, along with comments from federal agencies and the Science Advisory Board (SAB) review, provided additional ideas for and improvements in the framework.

MAP Stakeholder Input

In February 2002, a 1-day meeting was convened to gather stakeholder input to help EPA formulate the MAP for developing this Framework. Specifically, EPA solicited input on the following questions and received the responses identified after each question. To the extent practical, EPA incorporated these suggestions into the development of the MAP.

1. ***What organizing principles should the Framework follow?***

   The Framework should provide a basis for identifying and prioritizing potentially unreasonable risks to the environment that may be posed by some metals and metals species that is capable of discriminating among metals, metal alloys, and other metal compounds with respect to hazard and risk.

   The Framework should be developed using sound science and be flexible enough to allow for the inclusion of new methods and models as the understanding of factors that affect the fate, transport, bioavailability, and toxicity of metal substances increases.

   The Framework should use a tiered approach to accommodate differences in purpose and availability of data.

   The Framework should recognize that consideration of "inherent toxicity" alone has limited meaning with respect to metals and metal compounds, because whether an inherently toxic metal will actually induce toxicity depends on the extent of exposure and bioavailability.

2. ***What scientific issues should the Framework address and what methods and models should be considered for inclusion in the Framework?***

   Criteria and models properly incorporated into the Framework should reflect the critical importance of speciation, transformation, and bioavailability.

   Alternative approaches for assessing bioaccumulation should be considered.

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A determination should be made of what is considered significant bioaccumulation of metals in human beings.

Substances and elements should be differentiated from each other.

3. ***What specific steps should be taken to further involve the public and the scientific community in the development of the Framework?***

EPA should employ a variety of formal and informal mechanisms to further involve the public and the scientific community in the development of the Framework. Mechanisms suggested include scientific workshops, Federal Register notices, a Web site, and formation of cross-organizational work groups.

Scientific Advisory Board (SAB) Review

In September 2002, EPA's SAB reviewed the MAP and provided comments. The Panel's recommendations are summarized below.

1. The Panel agrees that metals should be assessed differently from organic pollutants in a number of contexts. Metals are elements and, although they do not degrade, they do have complex environmental chemistry. Moreover, some metals are essential for living organisms, and metals occur naturally in the environment.

2. The Panel agrees that the issues of chemical speciation, bioavailability, bioaccumulation, and toxicity are key issues in assessing the hazards of metals, with the following qualifications:

    - The Panel recommends that metal speciation be considered broadly under the umbrella of environmental chemistry. Understanding chemical speciation with regard to which forms are most toxic is clearly important. However, it is also important to understand the processes that regulate the rate of formation, stability, and prevalence of these metal species.

    - Although bioaccumulation data are useful for site-specific assessment of risk, bioaccumulation metrics such as bioconcentration factor/bioavailability factor measures can be problematic for assessing generic metal ranking. In as much as bioavailability incorporates the propensity of metals to transfer up trophic levels and the potential for toxicity exposure, the Panel suggests that bioavailability may be a better scientific focus issue than bioaccumulation for assessing risk and hazard to receptors.

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3. The Panel recommends consideration of stability and environmental residences time, as well as overall environmental chemistry, to determine temporal characteristics of metal hazards.

4. The Panel recommends greater emphasis on the combined effects of metals, including nutritional as well as toxicological considerations. The scientific foundation for such assessments is under development, and EPA should begin to think now about these considerations.

5. The Panel recommends that the differences between assessments for ecosystems and assessments for human health be clarified and highlighted in the Framework and the guidance document. The important factors in human health assessments are often quite different from those in ecosystem assessments.

6. The guidance document appears to focus on hazard ranking more than on risk ranking. If so, this should be made clear and the term "risk" should not be confused with "hazard."

7. In evaluating risk, it is also necessary to consider exposure. The Panel recommends greater emphasis on exposure in the Framework. In the development of the metal assessment, EPA should examine approaches to incorporate public health and environmental and ecosystem surveillance data in the metal risk assessment.

8. The Panel recommends that in the development of the Framework and the guidance document there be extensive consultation with the scientific community, stakeholders, and intended users, including risk assessors in other federal agencies, in different regions, and in the states.

Issue Paper Topics and Science Questions

Issue papers were developed to discuss unique risk assessment topics with respect to inorganic metals. Each paper was asked to discuss key topics, application within a decision making context, suggested Framework-specific language, and research needs. The papers are available at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=59052. The topics and primary questions addressed by the papers are:

- Environmental chemistry: How can environmental chemistry be better incorporated into assessments for inorganic metals?

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- Bioavailability and bioaccumulation of metals: What methods or tools can be used now to reflect metal bioavailability? What scientifically based approaches can be used to determine metal bioaccumulation?

- Metal exposure assessment: What are the relevant exposure pathways for inorganic metals to humans and ecological endpoints?

- Human health effects: What populations are most susceptible to effects from inorganic metals? How should toxicity tests be conducted and interpreted, including issues of essential elements, dietary salts, etc.

- Ecological effects: What ecological system characteristics promote increased toxicity from metals?

Peer Consultation and Framework Review

The next steps in the development of this document will be receiving comments from EPA staff and a peer input workshop. After revisions have been made to the document, a draft report will be sent for interagency review and review by the EPA Scientific Advisory Board (SAB).

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1.0. INTRODUCTION

Assessment of metals and metal compounds raises issues not generally encountered with organic chemicals. For example, metals are neither created nor destroyed by biological and chemical processes; rather, they are transformed from one chemical species to another. Metal elements and some inorganic metal compounds are not readily soluble, and as a result, toxicity tests based on soluble salts may overestimate the bioavailability and subsequent toxicity of these substances.

Some metals are essential elements at low levels but toxic at higher levels (e.g., copper, selenium, and zinc), whereas others that are nonessential may bioaccumulate and are toxic (e.g., lead, arsenic, and mercury). Many organisms appear to have developed mechanisms to regulate accumulation of some metals to some extent, especially essential metals. In addition, each environmental form of the metal has its unique fate/transport, bioavailability, bioaccumulation, and toxicity characteristics.

These and other metal-specific attributes can significantly affect the outcome of risk assessment. Because the majority of the compounds assessed by the U.S. Environmental Protection Agency (EPA, or the Agency) are organic substances rather than inorganic metallics, the various guidance documents provided for risk assessments of either human health or ecological receptors are lacking in specificity on how to account for metal attributes.

The Agency developed this framework document to supplement previous guidance for use in site-specific risk assessments, criteria derivation, ranking or categorization, and other similar Agency activities related to metals. This framework document will not be a prescriptive guide on how any particular type of assessment should be conducted within an US EPA program office. Rather, it is intended to make recommendations and foster the consistent application of methods and data to metals risk assessment in consideration of the unique properties of metals.

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1.1. PURPOSE AND AUDIENCE

The metals risk assessment framework describes basic principles to be considered in assessing risks posed by metals and presents a consistent approach for use across the Agency when conducting these assessments. While the audience for the framework is primarily intended to be Agency risk assessors, it will also serve to communicate principles, tools, and recommendations for metal risk assessment to stakeholders and the public.

The metals framework is intended 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 non-binding statement of policy. EPA believes that the metals framework provides a sound, up-to-date presentation of principles, tools, and recommendations for assessing the risk posed by metals, and serves to enhance the application of the best available science in Agency risk assessments. However, metals risk assessments may be conducted by EPA using approaches and tools differently than described in the framework for many reasons, including, but not limited to, new information, new scientific understandings, or new science policy judgements. The science surrounding metals risk assessment continues to be intensively studied, and thus is rapidly evolving. Specific principles, tools, or recommendations presented in the framework may become outdated or may otherwise require modification to reflect the best available science. Application of this framework in future metals risk assessments will be based on decisions by EPA that its approaches are suitable and appropriate. These judgements will be tested and examined through peer review, and any risk analysis will be modified as deemed appropriate.

1.2. FRAMEWORK SCOPE

The Metals Framework is a science-based document that focuses on the special attributes and behaviors of metals and metal compounds affecting human health and ecological risk assessments. It does not put forward a step by step process to assess the risk of metals to human health or the environment, but focuses on principles, tools and methods, coupled with recommendations to guide assessors to address the unique properties of inorganic metals. It

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supplements existing guidance and does not cover elements of the risk assessment process that are not unique to metals, as these are adequately addressed in other Agency guidelines and strategies (e.g., U.S. EPA, 2003a, U.S. EPA, 2000a, EPA 1998).

The Agency regulates metals and their inorganic and organometallic compounds because they have the potential to harm human health and the environment. The Agency's Science Advisory Board (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 for specific cases. Because organometallic compounds exhibit properties common to both organic substances and inorganic metal compounds, the properties of both the organic moieties of these compounds and their inorganic components would need to be addressed. Frameworks and associated guidance documents for assessing properties of organic compounds have already been developed by EPA and do not need to be discussed further here. Therefore, this document addresses only those 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 risk assessment issues thereof.

Metals and Metalloids of Interest

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

For the purpose of this document, the term "metals" generally refers to metals and metalloids that may pose a toxic hazard and are currently of primary interest to EPA. However, the principles and approaches put forth in the Framework are applicable to all metals. In some instances, metal-by-metal considerations are included, either as examples or to highlight particular exceptions.

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1.3. PRINCIPLES OF METALS RISK ASSESSMENT

One of the purposes of this document is to present key principles that differentiate inorganic metals from other chemicals when assessing their risk to human health and the environment. The MAP, the SAB and stakeholders, and various authors have discussed issues on the assessment of metals. The following list of principles concisely describes unique aspects of inorganic metals that need to be considered when risk assessments are conducted. Most of the principles focus on unique aspects of inorganic metals; a few stress important aspects of the risk assessment process where decisions are made that determine the degree to which a given metal issue (e.g., bioavailability) can be addressed in a given assessment or Agency program process. These principles should be addressed and incorporated into metals risk assessment to the extent practicable. They are visible throughout this document, in Sections 2 and 3, where specific topics are discussed, and in Section 4, where the principles are expanded upon with recommendations to guide assessors.

- **Environmental Chemistry** – The environmental chemistry of metals strongly influence their fate and effects on human and ecological receptors.

- **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.

- **Background concentrations** – Background concentrations of metals in soils and waters are partially responsible for limiting species distributions of plants, wildlife, and aquatic organisms.

- **Bioavailability** – The bioavailability of metals, and consequently the associated risk, varies 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

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assessments. In situations where data or models are insufficient to rigorously address bioavailability, the assumptions made regarding bioavailability need to be clearly articulated in the assessment.

- **Acclimation, adaptation, and environmental background concentrations** – Metals naturally occur at a range of environmental concentrations that can span five orders of magnitude and are influenced by local biogeochemical controls on metal cycling. Within limits, some organisms have developed mechanisms for coping with excess metals exposure (e.g., acclimation, adaptation). Only the bioavailable fraction of background concentrations contribute to total metal exposure and overall risk. Test organisms need to be acclimated to background conditions, and appropriately adapted organisms should be used for site-specific assessments.

- **Bioaccumulation** – 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 of bioaccumulation are used (e.g., BAF, BCF). Therefore, when incorporating bioaccumulation into metals assessments, the assumptions and uncertainty associated with the applicable bioaccumulation model(s) need to be critically evaluated and articulated.

- **Toxicity** – Due to limitations in available data and test methods, application of laboratory-derived toxicity data often requires extrapolation of results across test species, metal compound, 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 must be set at levels higher than required daily intake.

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- **Mixtures** – Metals may interact either synergistically, additively, or negatively in various ways, depending on the metal(s) combinations. All assessments have multiple metals, as they occur naturally and several are known to be essential micronutrients.

- **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 need to be specifically identified in the conceptual model for all metals assessments.

- **Assessment Goals and Scope** – 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 can be incorporated into an assessment. The degree to which the assessment goal(s), assessment scope, and other factors limit the incorporation of these principles needs to be clearly articulated in metals assessments.

1.4. RISK ASSESSMENT FRAMEWORK

Risk assessment provides a qualitative and quantitative comparison of the relationship between environmental exposures and effects in exposed individuals and other organisms. In 1983, the National Research Council (NRC) described four primary steps in the process of risk assessment, i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization. Ecological risk assessment (EPA, 1998) developed a similar framework which included problem

The Metals Framework works within the major phases envisioned in EPA risk assessment guidance:

✓ Planning

✓ Problem Formulation

✓ Analysis

✓ Risk Characterization

Scientifically sound metals assessments consider the unique properties and principles for metals

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formulation. This framework document for conducting metals risk assessment follows the principles and elements of human health and ecological risk assessment guidance developed by the U.S. EPA in the recent past (e.g., EPA, 1998; EPA, 2000a; EPA, 2003a).

The right side of Figure 1 illustrates the key scientific principles for the assessment of inorganic metals, environmental chemistry, bioavailability, essentiality, and background, which need to be considered in every phase of the risk assessment- risk management process. An effective risk assessment for metals will consider the unique aspects of metals, as formulated in the key metals concepts and principles, which differentiate them from other substances. Risk assessment is an iterative, rather than linear, process, and as such, it is important to consider the key concepts and principles for metals early and throughout the risk assessment process.

The importance of the incorporation of the metals principles into the conceptual model is emphasized in Figure 1 (left side). The conceptual model, discussed in Section 2.1 and presented in Figure 2, is a representation of the actual and potential, direct and indirect relationships between stressors in the environment and exposed humans (or particular sub-populations) or ecological entities. The application of methods and tools applicable to assess the exposure and effects of inorganic metals occurs in the analysis phase. In risk characterization and risk management, the incorporation of metals principles, such as, environmental chemistry, ecoregions, bioavailability, may depend on the national or site specific scope of the assessment.

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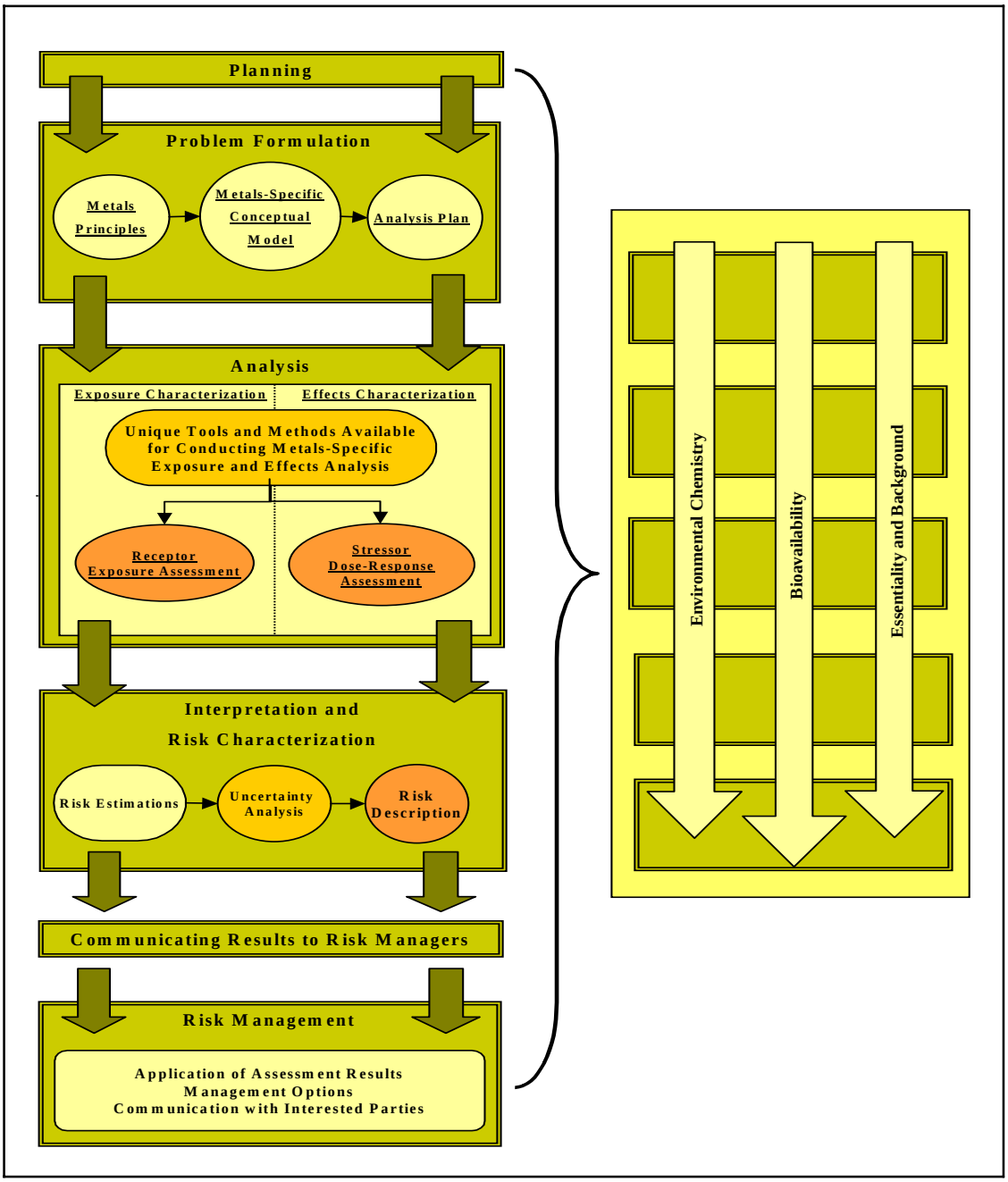

Figure 1. Risk Assessment/Risk Management Paradigm for Metals

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1.5. METALS ASSESSMENT CONTEXT

The context for the risk assessment is a major factor in determining the type of analysis that is appropriate for any particular situation. To provide a context for discussion of the Framework principles for metals, EPA has defined three general categories of assessments: (1) national ranking and categorization, (2) national assessments, and (3) site-specific assessments. Each of these types of assessment can vary in level of detail from simple screening analysis to highly complex study.

1.5.1. National Ranking and Categorization

In the first type of assessment, EPA must rank or categorize chemicals on the basis of their potential to cause risk. For many chemicals, there are significant data gaps regarding their chemistry, environmental fate, toxicity, or exposure potential. Nonetheless, EPA is tasked with protecting human health and the environment from the potentially harmful effects of these chemicals and thus had to develop methods to identify those most likely to pose a significant threat.

With more than 80,000 chemicals currently listed on the Toxic Substances Control Act (TSCA) inventory that can legally be used in commerce within the United States (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, there is a need for methods that rapidly screen chemicals for placement on lists or for prioritization of potentially hazardous substances.

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 risk. Example attributes include 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 accumulate in the food chain. Other methods, which may be less quantitative, rely more on a combination of expert judgement, stakeholder input, and availability of information to determine the priority or categorization of chemicals for decision making or other action.

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A few examples of programs where EPA identifies or categorizes chemicals for priority action include:

- Selecting chemicals for the Agency's Toxicity Characteristic regulation that defines hazardous wastes;
- Establishing reporting thresholds for spills of hazardous materials under Superfund;
- Setting priorities for revisions to the Ambient Water Quality Criteria (AWQA);
- Setting priorities for reregistration of pesticides;
- 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 it does provide an indication of the kinds of activities that EPA conducts in this regard. In addition, the Agency must set national standards and guidelines for specific chemicals, including metals, as described in the next section.

Prioritization of Pesticide Chemicals for Reregistration

The 1988 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA '88) require EPA to conduct a comprehensive review of all "older" pesticide active ingredients (i.e., those initially registered before November 1, 1984) to consider their health and environmental effects and to make decisions about their future use. A number of pesticide active ingredients were originally registered many years ago, when health and safety standards were not as stringent as the current standards. Through the Pesticide Reregistration program, EPA is ensuring that older pesticides meet contemporary health and safety standards and product labeling requirements and that their risks are mitigated.

To prioritize the ongoing reregistration review of approximately 1150 older pesticide active ingredients, FIFRA '88 directed EPA to divide these pesticides into four lists (A, B, C, and D) so that those that might potentially pose the greatest risk would be reviewed first. These lists were developed as follows:

List A contains most food-use pesticides, because they have the greatest potential for exposure across the general population.

Lists B, C, and D contain the remaining pesticides, categorized on the basis of such factors as potential for residues to be found in food or drinking water, potential for worker exposure, the potential severity of unintended adverse effects to animals and plants, and restricted use status.

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1.5.2. 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 [RCRA], residual risk determinations under the Clean Air Act (CAA), pesticide registrations). 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 emissions, 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

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 physical, chemical, and biological integrity of waters of the United States. 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) (U.S. EPA, 2000b; DiToro et al., 2001; Santore et al., 2001). This model, which is described in further detail in Section 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.

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biogeochemistry of metals, making it difficult to set single-value national criteria (national standards that apply at the point of exposure, such as MCLs, are less affected by these factors). In order to do such assessments, there are several approaches the Agency commonly undertakes. 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 conservative enough 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 of the factors that may affect potential risk, including environmental factors affecting the fate, transport, exposure potential, and toxicity of the chemicals released.

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

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 those 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 groundwater. It then models the fate and transport of those constituents to potential receptors.

The fate and transport of a constituent is dependent on environmental conditions, and many of the waste streams of concern are generated in many different locations with varying meteorology, soil characteristics, groundwater movement, surface water flows, and other environmental factors. The Agency must take this variability into account in determining whether the waste is likely to pose a threat to human health and the environment.

The current practice in the hazardous waste listing program is to develop distributions that describe this variability either nationally or across the geographic areas where the industry being studied is located. These distributions, along with distributions of exposure factors, such as ingestion rates, and distributions of waste stream characteristics, such as volume and constituent concentrations, are then input to the Agency's fate, transport, and exposure models in a probabilistic manner to provide a distribution of the potential risks to human and ecological receptors. The Agency's decisionmakers can then look at points of interest on the risk distribution in making its decision on whether to designate the waste as hazardous.

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by parameter distributions used as inputs to the probability analysis procedure. The result is an integrated distribution of potential risk levels. The difficulties in conducting this kind of analysis are in developing appropriate distributions for each of the parameters 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.

1.5.3. Site-specific Assessments

Site-specific assessments are conducted to inform a decision concerning a particular location and may also support some national regulatory decisions. Examples include:

- Determining appropriate soil cleanup levels at a Superfund site,
- Establishing water discharge permit conditions to meet ambient water quality standards, and
- Determining the extent of air emission controls needed to meet ambient air quality standards.

An accurate site-specific assessment for a metal may require knowledge of the form of the metal as it enters the environment, the environmental conditions affecting the metal

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, then more stringent limits are developed to ensure that those standards are met.

The water quality standards are established by the states and consist of a designated use for the waterbody 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 chemical(s) of concern and then setting the allowable discharges to ensure that the criteria for the chemical(s) is (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.

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(climatological conditions, soil geochemistry, water and sediment chemistry, etc.), the existence of plants and/or animals that might accumulate the metal 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 it reaches that organism. Although many of these same factors 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.

In summary, the Agency conducts a variety of assessments, from site-specific risk assessments to national criteria setting and ranking. All of these assessments share common elements and rely on accurate information and knowledge about how chemicals behave in the environment and when they come in contact with humans or other organism of concern. Metals have unique environmental and toxicological properties that may confound such assessments if they are not given consideration. This Framework provides the basic tools for application in each of these programmatic contexts so that metals assessments can be conducted with the same rigor, precision, and accuracy as assessments for organic substances.

1.6. ORGANIZATION OF METALS FRAMEWORK

The Framework is loosely organized around the risk assessment paradigm. It begins with a discussion of problem formulation (Section 2) to frame the issues to be discussed. A conceptual model is presented that highlights the areas where metal-specific information is required to move through the risk assessment, criteria development, or classification/ranking process. This discussion provides additional direction to where in the document the guidance material is discussed for each issue identified. Also in Section 2, a conceptual model on bioavailability is presented (Drexler, et al., 2003) along with definitions developed by the issue papers authors.

The detailed discussion of metal-specific issues occurs in Section 3, where each subsection is devoted to a particular metals issue. Specifically:

- Section 3.1 – Environmental Chemistry
- Section 3.2 – Exposure

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- Section 3.3 – Ecological Effects
- Section 3.4 – Human Health Effects

For each issue, a brief description of the concepts to be addressed is presented, with reference given to existing issue papers that cover it in greater depth. This is followed by a presentation of currently available methods for developing the needed information, either from look-up tables, default values, appropriate models, or other sources. Each subsection concludes with a brief discussion of the limitations of current methods, any new methodology currently under development, and a suggestion of where improvements in the process could be made in the future.

It is important to stress that Section 3 does not precisely follow the risk assessment framework of exposure assessment and effects assessment, but rather presents all the necessary metal-specific attributes to consider when conducting a hazard and risk assessment. This is because several of the issues are cross-cutting (e.g., Environmental Chemistry discussions in Section 3.1) and may have application to both exposure and effects assessments. Furthermore, because this Framework addresses only those aspects of the risk or hazard assessment that are specific to metals, it does not provide a comprehensive overview of the entire process. Once the technical details are understood, the challenge then becomes one of incorporating them into EPA decision making processes.

Section 4 takes this up with an explicit discussion of application of each issue to the three assessment levels of primary Agency concern (site specific assessments, national scale assessments, and classification/ranking). Recommendations are made to incorporate metal specific issues into the phases and tiers of risk assessment. A discussion is included about which tools are applicable to screening-level assessments and which information is most useful for detailed, in-depth analyses.

The document concludes with a discussion about research underway, planned, and needed to reduce uncertainty (Section 5). Although our understanding about metals issues is broad based, specific methods and data are more readily available in some areas (e.g., fresh water ecosystems) than in others (e.g., soils). This section highlights those areas where active research is expected to move the science forward within the next 5 years and identifies other aspects that are in need of further attention. The need for continued research and development of

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metals-specific risk assessment methodology should in no way detract from the expectation of applying sound science to our current way of doing business, as the Framework provides substantial guidance on enhancements to the process that can be done with currently available information.

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2.0. PROBLEM FORMULATION

Metals are naturally occurring constituents of the environment, and, consequently, biota have evolved in the presence of metals. 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 use of landscapes. For example, metal-sensitive organisms are not likely to be found occurring naturally in areas of calciferous soils where the low pH increases metal bioavailability. Furthermore, response of organisms to the "added risk" of elevated metals differs, depending on their adaptation to naturally occurring background metals concentrations (see Section 3.4. Ecological Effects). Therefore, during the problem formulation phase of an assessment of risks of anthropogenically elevated metals, it is important to clearly define the geospatial location of the area to which the results will apply and to identify environmental controlling factors (e.g., pH, organic matter, iron, aluminum) (see Section 3.1. Environmental Chemistry) and the resulting naturally occurring differences in biota composition and metal sensitivity.

For site-specific assessments, there generally will be only a single area of concern, and the assessment results will be directly applicable to the entire range of species that may be found on that site (although it is important that the problem formulation identify these species to focus the remainder of the assessment). For assessments conducted for regional or national assessments, criteria development, or ranking purposes, the use of results that are overprotective of most areas in order to be adequate for highly sensitive species with limited distributions should be acknowledged. It is recommended that, when possible, such 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.

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This is directly analogous to the use of ecoregions when establishing water quality criteria (WQC) (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 must be considered are not geospatially correlated. Rather, consideration needs to 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 3.3 on human health effects). Again, the problem formulation must 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.

2.1. METALS CONCEPTUAL MODEL

A conceptual model shows the interrelationship between the metals or metal compounds of interest and the assessment endpoints. Endpoints are selected during problem formulation for their relevance to management goals, societal values and laws, known adverse effects of metals, and endpoints of importance to stakeholders. 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.

Areas in the conceptual model that stand out as metal-specific issues are identified in Figure 2 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,

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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. The conceptual model (see Figure 2) identifies the issues and where within the risk assessment process they occur. It helps direct the remainder of the assessment.

2.1.1. Metal-Specific Attributes

This section identifies metal-specific attributes of the various parts of the risk assessment conceptual model. The lettered number in parenthesis in each paragraph refers to a transition point in Figure 2 and indicates where within the process a particular concept should be applied.

- **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 needed 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 due to the variable solubility of metal complexes, essentiality of some metals for organismal functions, and naturally evolved process for uptake, sequestration, or exclusion of these materials.

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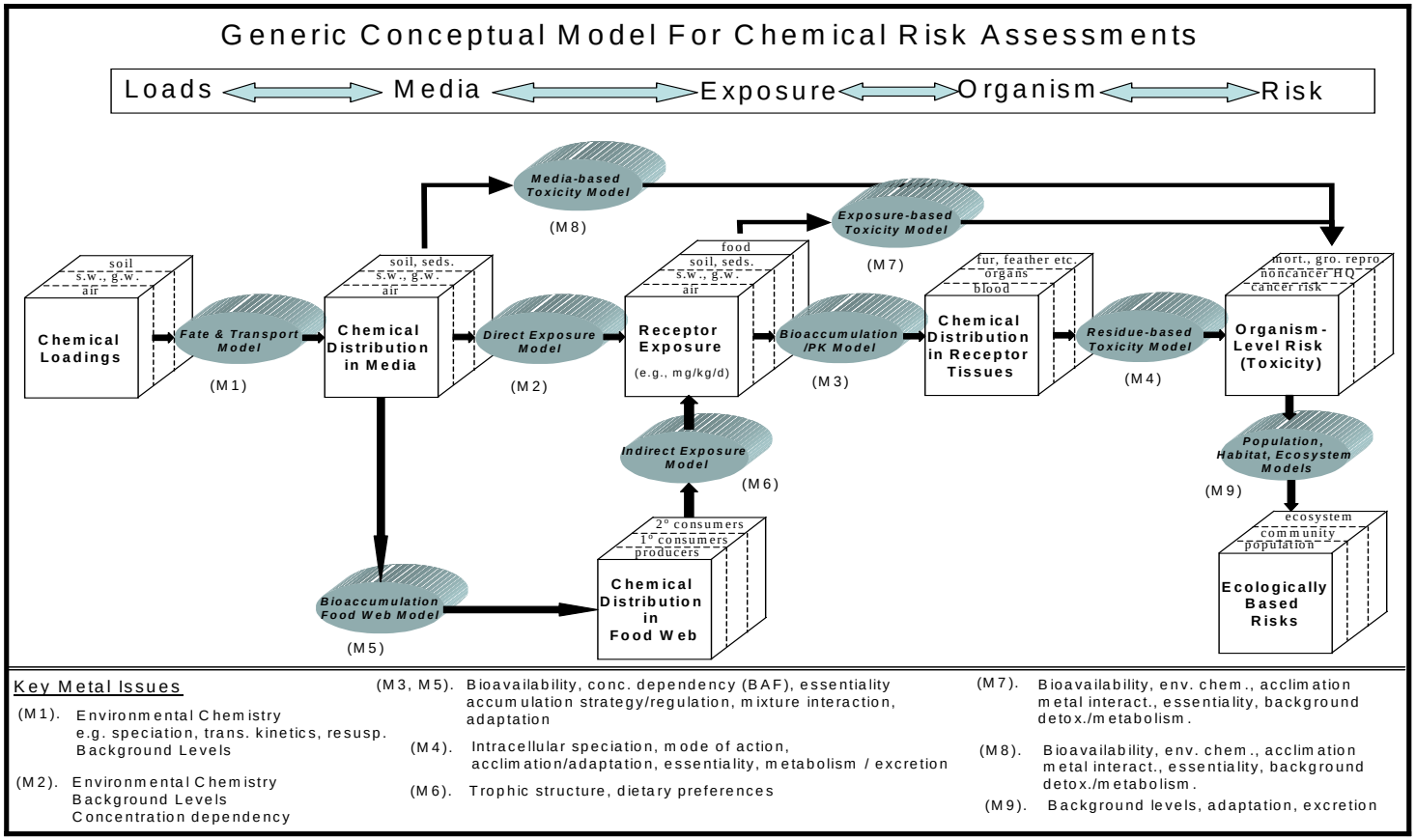

Figure 2. Generic Conceptual Model for Metals Risk Assessment

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- **Bioaccumulation/physiologically based toxicokinetic (PBTK) models (M3).** Whereas many organic substances require metabolic activation to become toxic or, conversely, to be detoxified and excreted, metals do not. Metals may complex with proteins or other carrier molecules to distribute to target organs or for sequestration and excretion. They typically do not bioaccumulate or biomagnify within whole organism, although they may do so in particular tissues (e.g., lead in bone or cadmium in kidneys). Furthermore, the amount of metal taken up from the 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 needs to be understood, either from empirical data or PBTK models. Because of the processes discussed in the previous paragraph, this can be particularly challenging for metals. Species of metal in the exposure matrix can significantly influence this relationship because uptake and organ distribution kinetics are likely to differ.
- **Bioaccumulation/Food web model (M5).** This node of a conceptual model applies to ecological risk assessments and, to a lesser extent, human health

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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, there are some metal-specific generalities about the relative importance of exposure pathways that 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 data must 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. Information about RBA, trophic transfer rates, dietary preferences, natural background concentrations, and organism adaptations is required 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 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 one of the fundamental determinants and delimiters of ecoregions (in conjunction with climate, elevation, and day length

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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.

2.2. BIOAVAILABILITY, CONCEPTUAL FRAMEWORK, DEFINITIONS[1]

The bioaccessibility, bioavailability, and bioaccumulation properties of inorganic metals in soil, sediments, and aquatic systems are complex. As with organic compounds, 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.

Metals differ from organic compounds in that they can be present as different species, with the parent element associating with different ligands but never being irreversibly transformed or metabolized. To better characterize the risk to human and ecological receptors presented by metals in the environment, the processes that affect metal speciation and the effects of speciation on metal bioavailability, both in the external environment and within an organism, must be understood and quantified. The need to consistently and accurately measure quantitative differences in bioavailability between multiple forms of inorganic metals in the environment poses a major challenge for EPA. Understanding metal bioaccumulation in relation to potential impacts also poses a major challenge for the Agency.

Once absorbed or assimilated into biota, metals are subject to the same variety of fate processes as organic substances, including storage, metabolism, elimination, and accumulation. Although organic compounds may be metabolized within an organism, with the parent compound decreasing over time, metals do not change form. Degradation products of organic substances are usually less toxic than the parent compound, although in some cases they may become more toxic (e.g., carcinogenic polycyclic aromatic hydrocarbons). With metal compounds, the metal ion may bind to a wide variety of molecules in the organism that are

[1]The information in this subsection is extracted directly from the metals issue paper covering bioavailability and bioaccumulation of metals. This issue paper can be found on the EPA website at: http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=59052.

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essential to cellular function (e.g., enzymes, structural proteins), altering their function and causing toxicity.

Many toxic metals become associated with sulfur-rich proteins, particularly Class B metals (e.g., Hg, Ag). In some cases, metals bind to proteins or other molecules that are not bioactive and can prevent toxicity through regulating the amount of metal present in cells or inhibiting binding to active receptors. Examples include metallothioneins, phytochelatins, and cysteine-rich compounds. Metals may also be precipitated in phosphate or sulfide bodies within cells, thereby sequestering them and preventing mobility and subsequent toxicity. This issue has been reviewed by Mason and Jenkins (1995) and George (1990).

Organisms have evolved in the presence of metals and, in many cases, have developed appropriate strategies of metal metabolism (homeostasis) when concentrations exceed those normally encountered by the organism. In contrast, most organic contaminants typically are novel compounds that have never been experienced during the evolutionary history of organisms; hence, they represent unique challenges to the organisms because no specific sequestration or detoxification strategies have evolved. However, several generic (oxidative and conjugative) metabolic pathways exist that usually succeed in increasing the hydrophilicity of most organic compounds to facilitate elimination from the body.

2.2.1. Conceptual Framework

A conceptual framework of metals bioavailability and bioaccumulation is presented in Figure 3. In this diagram, metals in exposure media partition between an aqueous phase and a solid (particulate) phases. In the aqueous phase, speciation—as influenced by inorganic (e.g., pH) and organic (e.g., DOC) modifying factors—is a key factor in determining the forms (species) of the dissolved metal that are available for uptake. Other modifying factors (e.g., competing cations) also influence uptake (via competition) at the biological surface (respiratory, gut, or root tip). Note that dietary uptake of metals is shown in a relatively simplified manner. Bioavailability of metal in the gut is similarly influenced by modifying factors that are part of the digestive process.

Once adsorbed and then absorbed into and across the biological surface, metal is distributed throughout the organism. This process of distribution can be exceptionally complex, and the primary issue for consideration is metal/biomolecule interactions at receptor sites that

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result in effects (i.e., accumulation at the site of toxic action). Additionally, bioaccumulated metal can also serve as a source of exposure in terms of trophic transfer. Note that the diagram in Figure 4 applies generally to both aquatic and terrestrial systems, including sediments, although the relative importance of specific factors and pathways will vary considerably. Similarly, within an exposure medium, differences in organism morphology, physiology, and behavior can add variability.

2.2.2. Definitions

As illustrated in Table 1-1 of the National Research Council (NRC) document, *Bioavailability of Contaminants in Soils and Sediments: Processes, Tools, and Applications* (NAS, 2002), many variations of terms and definitions are used for the concept of "bioavailability." The NRC report does a good job of reviewing the history and nuances of the various terms and meanings involving "bioavailability processes." However, the bioavailability issue paper authors (Drexler et al., 2003) provided EPA with some practical, standard, and defensible recommendations on concepts, terms, and definitions that can serve as a paradigm for studying metals and their "bioavailability."

From that perspective, they proposed that the following definitions might serve EPA risk assessors and risk managers best for their needs in addressing some of the myriad problems involved with bioavailability and bioaccumulation of metals in the environment. It is noted that although definitions are often discussed in terms of both terrestrial as well as aquatic systems, some are more applicable to one media type than to the other.

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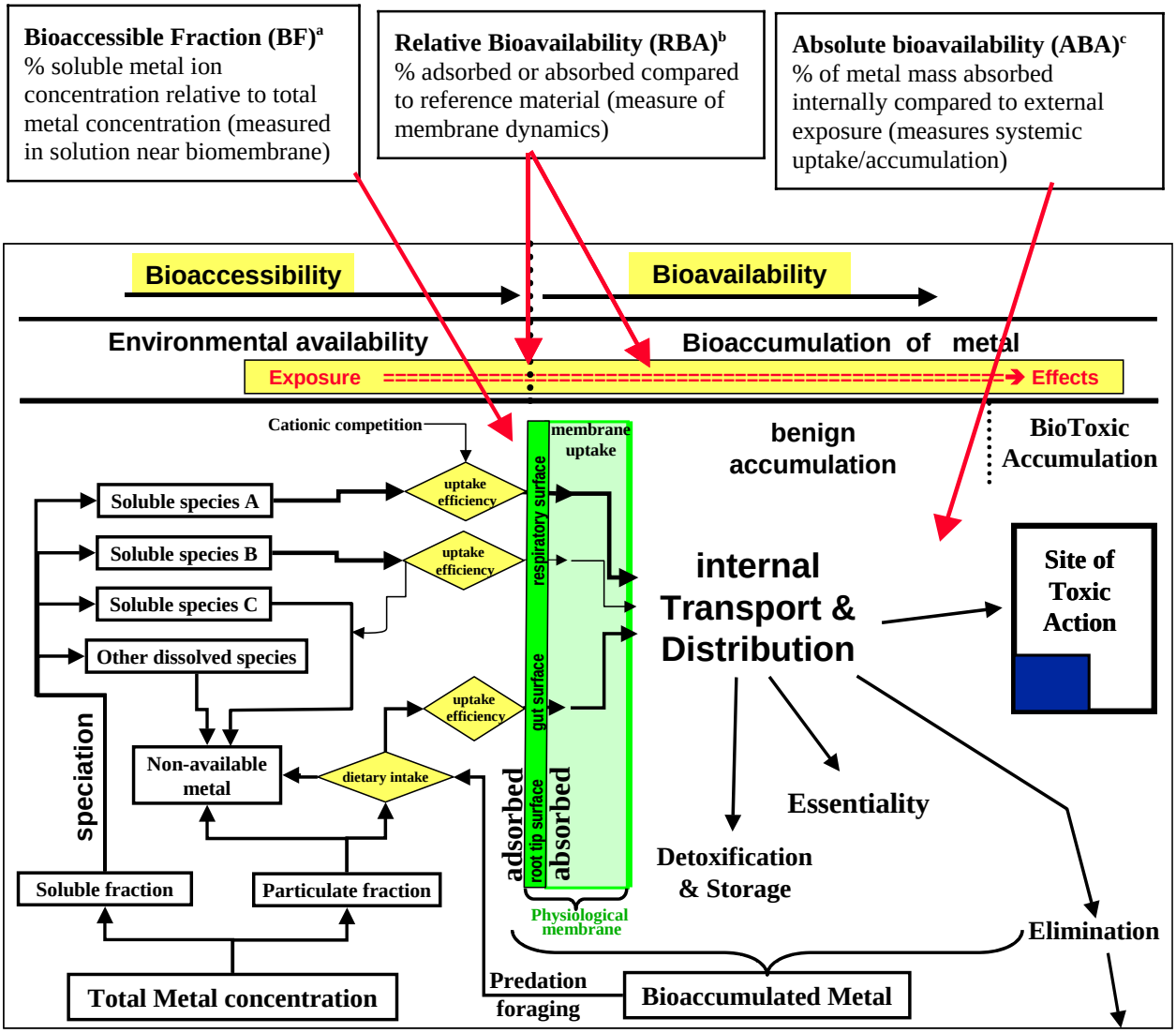

Figure 3. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems.

[a]BF is often measured as an in vitro method and must be validated using 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.

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2.2.2.1. 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 (Figure 4).

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 Cu is available for interaction with the gills of a sediment-dwelling invertebrate, binding to DOM, and advective transport, whereas Cu 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 Cu into the water column, making it environmentally available.

2.2.2.2. 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; however, the focus of this document is mainly on the inorganic species. 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. EPA assumes that, by default, the RBA of metals is 100% unless reliable data are available to convince otherwise and permit the lowering of this default value to a more realistic value.

The U.S. Food and Drug Administration (FDA) has been evaluating bioavailability of drugs, including metals, for decades in animals and humans and currently uses this definition in the 2002 FDA guidelines (CFR § 320.1):

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> *...the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.*

The following definition is similar to the one used by FDA and is proposed as a working definition for EPA for use in risk assessment and risk management:

> *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.*

Although bioavailability may be a defined measurement when considered in vertebrate animals whose metal uptake is directly a function of the concentration of metal in the diet, it is not as easily defined in aquatic and terrestrial organisms whose food consumption is difficult to measure. Furthermore, metals are present in the ambient 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 measurable parameter.

Relative bioavailability (RBA). RBA (Figure 3) of a metal is the ratio (fraction or percentage) of the amount of a metal substance of interest that is adsorbed or absorbed under defined conditions (e.g., metal salt type, specified vehicle or matrix, differing test doses, different physiological states of the receptor) as compared to a reference metal substance tested under standard conditions. The RBA is usually the most often employed and readily measured adjustment for bioavailability in risk assessments of metals.

Relative absorption factor (RAF). RAF (Figure 3) is fairly synonymous with RBA, but it more specifically refers to the fraction or percentage of a metal that is absorbed across a biological membrane. The RAF is one of the more common measures of uptake of metals into the body from environmental exposure media. The value for RAF is properly calculated as a ratio of the amount (i.e., dose) of a reference metal salt (e.g., lead acetate) administered in a vehicle and the amount of metal (e.g., lead) administered in the test media that produced equal biological responses (e.g., area under the curve [AUC] for blood lead [PbB] concentrations).

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Note that it is critical to understand that the RAF—as well as estimates for absolute bioavailability—is valid only for the specified conditions of the study, with a particular metallic substance and the exact receptor tested, because minor experimental variations can result in major differences in RAF values (e.g., age and pregnancy make two- to fourfold differences in the RAF for adult vs. juvenile pig models for children).

Absolute bioavailability (ABA). ABA (Figure 3) is conventionally expressed as the fraction of the externally administered amount of a metal substance that is absorbed and reaches the systemic circulation or central compartment of the receptor. This is the usual definition that is associated with the administration of doses of metals to terrestrial vertebrates in laboratory situations. In humans and animal models, an intravenous administration of doses of the metal salt is used as the reference for 100% ABA, a soluble oral salt is administered at the same doses, and the fraction of systemic absorption is calculated to determine the ABA. The ABA is less often used in risk assessment and is somewhat more difficult to measure and apply as an adjustment factor for risk assessment purposes. For plants and lower animal forms, the ABA is typically not expressed as a fraction of an exposure dose, although this dose can be generated if a suitable reference (soluble) metal and suitable conditions are used to compare with the test metal and environmental conditions. Generally the ABA in wildlife has been used to refer to the total amount of metal represented by the whole body or tissue mass of metal under a given set of environmental conditions and is used for calculations of exposure, toxicity, and trophic transfers. (Above adapted from Drexler et al, 2003 IP)

2.2.3. National Research Council Report

The NRC report on bioavailability of contaminants in soils and sediments (NRC, 2002) provides a broad overview of chemical availability issues in environmental media and within biota. The metals framework in general, and this section specifically, responds to some of the NRC report's recommendations on making bioavailability processes visible in risk assessments and improving the scientific basis supporting bioavailability in risk assessments. For metals, where environmental chemistry and bioavailability are central issues, this documents puts forward principles and tools to be responsive to the NRC recommendations. The NRC report also lists various tools, with their strengths and limitations, that are applicable to evaluating bioavailability. Although the NRC report states a preference for mechanistic approaches, decisions must often be made using assumption and degrees of uncertainty. Tools or methods

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currently applied to bioavailability issues typically keep pace with scientific advancements in the field.

2.3. NEXT STEPS

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 (U.S. EPA, 1992; NRC, 1985). These hypotheses are then examined through analysis of data, 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.

The next section of this Framework lays out the metal-specific issues that need to be considered when conducting the analysis phase of an assessment and provides tools and associated guidance for doing so.

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3.0. METAL-SPECIFIC TOPICS AND METHODS

This section discusses metal specific topics and methods for assessors to utilize in the assessment of risk to humans and ecological entities from exposures to inorganic metals. It applies information and text from the metals issue papers, and reflects contributions by EPA scientists and external experts. The metals issue papers are available on the EPA internet website at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=59052.

Key topics and tools in this section are presented in subsections on environmental chemistry, exposure pathway analysis, human health effects, and ecological effects. The applications and limitations of the various models and methods for conducting metals assessments are presented to inform the reader. Topics and tools related to bioavailability and bioaccumulation are discussed throughout section 3, since they have far reaching impact that crosses many aspects of metals assessment.

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3.1. ENVIRONMENTAL CHEMISTRY

3.1.1. INTRODUCTION AND TERMINOLOGY[1]

The following discussion is a general review of factors pertaining to the chemistry of metals in sediments, soils, and waters in the context of risk assessment. Many generalities have been developed for hydrophobic organic compounds (HOCs) that allow the risk assessor to move forward with estimates of chemical fate, exposure, and effects. HOCs usually exist as single chemicals that are relatively unaffected by ambient chemistry. These chemicals have defined life times and a limited number of physical-chemical properties that can provide accurate estimates of their fate and effects.

Unlike HOCs, metals are persistent (do not degrade) and exist as multiple interconverting species, the exact mixture of which depends on ambient chemistry. Because the behavior of metals defies simple generalities, it is necessary to understand the chemistry of the particular metal and the environment of concern. However, we can generalize factors that control metal chemistry and environmental characteristics, where this generalization allows us to progress with estimates of metal fate and effects.

The **oxidation state** of a metal is often a significant feature of its speciation because of its impact on other processes. The well-known example of the high mobility of Cr(VI) compared with that of Cr(III) demonstrates the significance of the oxidation state. Toxicity depends on both the oxidation state and the form of a metal (as cation or anion) and its tendency to form complexes with ligands. For example, the toxicity of As(III) to aquatic life is significantly different from the toxicity of As(V). Cr(VI) is considered a known human inhalation carcinogen, whereas Cr(III) is generally considered to have low human toxicity. Cupric ion is more toxic to

[1]Langmuir et al., 2003.

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fish than is the cupric carbonate complex. Dimethyl mercury is generally thought to be more toxic and to have a greater bioaccumulation potential than mercuric chloride.

Mobility of metals in water, sediment, or soils is affected by a variety of factors. The ability of a metal to sorb to a substrate is usually the determining factor in its mobility. Physical adsorption—which is important for molecular organic compounds—is largely inapplicable to the sorption of the toxic trace metals, which are usually adsorbed as ionic species. Ion exchange, too, rarely applies, in part because of the relatively low concentrations of toxic metals compared with those of major ions. In fact, toxic metal adsorption is often relatively independent of the concentrations of the major ions. *Metal sorption is strongly pH-dependent and a function of metal complex formation and ionic strength.* The most accurate and mechanistic approach to modeling and predicting metal adsorption is surface complexation modeling, which ideally can account for all of these variables (Stumm and Morgan, 1996; Langmuir, 1997). Table 1 presents factors that are important to metal sorption in soils, aquifers, and sediments.

The degree of mobility of organic contaminants is often expressed by means of a single **partition coefficient** that describes the extent of equilibrium between sorbed and dissolved forms of a compound (U.S. EPA, 1995). Mobility is then calculated from the partition coefficient. Such an approach is applicable only to metal adsorption when the conditions listed above are practically constant, which is rarely the case. In fact, when metal adsorption is described using partition coefficients, the value of such coefficients typically needs to be varied by two or more orders of magnitude to reproduce metal adsorption behavior. This topic is discussed further in the ground water section.

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3.1.2. HARD AND SOFT ACIDS AND BASES – THE STABILITY OF COMPLEXES

Complexes are formed between metals (acids) and ligands (bases) both in solution and at the surfaces of minerals and of organisms. Toxic reaction of organisms to metals can be directly related to the nature of the metal complexes formed in solution and at the surface of the organism.

A useful definition that helps to explain the strength of metal complexing and metal toxicity is that of **hard and soft acids and bases (HSABs)** (Pearson, 1968). In this definition, cations are Lewis acids and ligands are Lewis bases, with the metal cation and ligand in a complex acting as electron acceptor and donor, respectively. **Soft** implies that the species' electron cloud is deformable or polarizable, with the electrons mobile and easily moved. Such species prefer to participate in covalent bonding.

> ***Hard acids and hard bases.*** Complexes formed between divalent hard acid cations and monovalent or divalent hard bases are ionic and relatively weak and are often termed "ion pairs." Complexes formed between Be^{2+} or trivalent hard acids and hard bases tend to be ionic and relatively strong.
>
> ***Soft acids and soft bases.*** Strong, relatively covalent bonds are formed in complexes between soft and borderline soft acid cations and soft bases. Ligand binding sites on the external or internal surfaces of organisms are often of soft base character and thus bond strongly with soft and borderline soft acid cations.

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Table 1. 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 and concentrations (activities) Dissolved organic carbon Ionic strength Temperature	Chemical identity Complexation chemistry Solubility Precipitation chemistry Redox behavior Vapor pressure

Hard species are comparatively rigid and nondeformable, have low polarizability, hold their electrons firmly, and prefer to participate in ionic bonds in complex formation (Langmuir, 1997). Neiboer and Richardson (1980) developed a simple categorization scheme based on metal thermodynamics that generalizes the binding affinity of metals: Class A metals, which include the alkali elements and alkaline earths as well as Ba^{2+}, Al^{3+} and Sr^{2+}; Class B metals, which include Ag, Au, Cu, Hg, Pd, Pt, Pb; and borderline metals, which include Sn, Cd, Co, Ni, Zn, Sb, As.

Class A metals are the least toxic and preferentially bind with oxygen, followed by nitrogen and sulphur. Binding is usually by means of ion exchange and is sensitive to pH. Many of these metals are macronutrients. In contrast, Class B metals show the opposite trend of binding preferentially with S, followed by N

Ligands are simply anions or molecules forming coordination complexes with metal ions. Depending on whether a ligand shares one, two, three or more electron pairs with metals, it is called a mono-, bi-, tri- or multidentate ligand. For ligands composed of more than one atom, the atom that directly participates in metal-ligand binding is called the donor or ligand atom.

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and O, and the binding exhibits more of a covalent and irreversible nature. Borderline metals exhibit more of a Class B nature in the following order: $Pb^{2+} > Cu^{2+} > Cd^{2+} > Co^{2+} \cong Fe^{2+} > Ni^{2+} > Zn^{2+} > Mn^{2+}$. The tendency to bind to a ligand or substrate follows the order of Class B metals, followed by Class A metals Pb, Cu, Cd, Zn > Ca > Mg >> Na (Pickering, 1986). Table 2 summarizes HSAB relationships for the metals of concern.

Table 2. Classification of Select Metal Ions as Hard (Class A), Soft (Class B), or Borderline Lewis Acids

Hard	Borderline	Soft
H^+, Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Al^{3+}, La^{3+}, As^{3+}	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}	Cu^+, Ag^+, Au^+, Tl^+, Hg^+, Cs^+, Pd^{2+}, Hg^{2+}, Pt^{2+}

Source: Adapted from Neiboer and Richardson (1980).

Dissolved metal ions range from soft to hard acids. Depending on a metal's HSAB qualities, it will bind to different degrees with one or more of a variety of soft to hard anions and neutral molecules. The consequence is that each metal dissolved in natural water will speciate among different forms, including the uncomplexed metal ion (aquated ion) and various metal-ligand complexes. As an example, the outer shell electrons of copper are stabilized in forming a complex with NH_3:

$$Cu^{2+} + 4NH_3 \rightarrow [Cu(NH_3)_4]^{2+}$$

This distribution of metal among dissolved complexes is important because, according to the **free ion activity model (FIAM)**, the concentration or activity of the free or aquated ion is generally the most biologically active form of the dissolved metal. It is also important because speciation can influence adsorption to solid phases or precipitation. As an example, coordination of Ca^{2+} with CO_3^{2-} to stabilize calcium's outer shell electron configuration produces a solid:

$$Ca^{2+} + CO_3^{2-} \rightarrow CaCO_3(s)$$

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Consequently, metals' tendencies to associate with important solid phases such as sediment sulfides can also be related to their fundamental qualities. For example, extremely insoluble metal sulfides are formed in anoxic sediments by very soft acid metal cations such as Hg^{2+} (log K_{sp} = –57.25) or Ag^{+} (log K_{sp} = –49.7), whereas less soft metals such as Mn^{2+} (log K_{sp} = –19.25) or Fe^{2+} (log K_{sp} = –22.39) form slightly more soluble metal sulfides.[2] These differences in solubilities are fundamental to the method of **acid-volatile sulfide (AVS) normalization of sediment-associated metals** (see discussion below on sediment chemistry). Finally, according to the BLM, effects of metals are related or correlated with metal interaction with biological ligands. Predictions of metal fate and effects are enhanced by understanding HSAB theory.

3.1.2.1. HSAB Metal Speciation, Fate, and Bioavailability

Toxic metals such as Zn^{2+} and Cd^{2+} may be blocked from binding to surfaces on biota (e.g., the gills) by hard acid metals such as Ca, Mg, and Na. Even though these hard acid metals bond weakly with the soft base sites on the surfaces of biota, their concentrations in most waters are typically a thousand times greater than those of the toxic metals, so that they overwhelm the toxic metals in competition for surface bonding sites. However, when metal is adsorbed to organic matter, the toxic metals, such as Cu^{2+} in particular, are strongly adsorbed independently of concentrations of the hard acid metals (Lu and Allen, 2002). Thus, Ca, Na, Mg, and the other hard acid metals are important when using the BLM to calculate potential toxicity to aquatic organisms from metals in the water column, but they are not important in considering bioavailability from soils or sediments.

In addition to predicting metal form and speciation, ligand binding tendencies can be used to predict bioaccumulation. Fisher (1986) used a metric of metal binding tendency with intermediate ligands (log $-K_{so}$ of MOH) to identify a trend in metal bioaccumulation for natural

[2]Solubility products for all metals except silver were obtained from Di Toro et al. (1990). The product for silver is from Stumm and Morgan (1970).

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phytoplankton. Fisher's underlying assumption was that metals bind to biological ligands on cell surfaces, including those with O donor atoms, and that trends in biological ligand binding are reflected in metal bioaccumulation factors (BAFs). Fisher also used these methods to estimate mean oceanographic residence times for diverse metals. Xue et al. (1988) correlated measured metal binding to algal surfaces with metal-ligand binding tendencies.

3.1.2.2. Application of HSAB to Metal Effects

Jones and Vaughn (1978) clearly demonstrated qualitative relationships between mouse LD50 values for divalent metals and HSAB-based qualities of metal-ligand binding. They proposed that it might be possible to estimate relative toxicity of a series of metals on the basis of HSAB qualities. Williams and Turner (1981)expanded and refined aspects of Jones and Vaughn's research, explicitly presenting regression models predicting rodent LD50 based on a softness metric.

In a series of publications (1996 to 2003), Newman and co-workers explored quantitative HSAB-based relationships for potential use in ecological risk assessment of metals. In ecological risk assessment activities, metal effects data are often missing for the biological species or media of interest. The ability to predict an effect level for an untested metal of interest from HSAB qualities and existing effects data for other metals will enhance the effectiveness of assessment activities. The quantitative structure-activity relationship (QSAR)- like models developed for metals were called quantitative ion character-activity relationships (QICARs). Newman and McCloskey (1996) and McCloskey et al. (1996) successfully developed QICARs using the Microtox bioluminescence assay for metals of similar and then differing charge. Figure 4 is an example of a QICAR model for mono-, di-, and trivalent metals based on one explanatory variable. The addition of a second explanatory variable improved predictions for metal ions differing in charge. Qualitative evidence in Newman and McCloskey (1996) suggests that divalent metal interaction in mixtures might also be predictable with QICARs.

These QICAR studies were successfully extended to exposures of a metazoan (*Caenorhabditis elegans*) to divalent species (Figure 5) and then to metals of differing charges

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(Tatara et al., 1997, 1998). Next, the general applicability of QICAR models for a wide range of effects was explored (Newman et al., 1998), leading to the conclusion that the approach was generally valid. The approach was recently integrated into the general context of modern QSAR practices by McKinney et al. (2000). Lewis et al. (2000) extended the QICAR theme to rodent mortality, and Weltje (2002) successfully applied it to the Lanthanides.

3.1.2.2.1. How HSAB-Based Methods Might be Used in Ecological Risk Assessments

The commonly applied FIAM and simultaneously extracted metal (SEM) AVS approaches have HSAB theory at their foundations. Fisher's model of intermetal trends in phytoplankton bioaccumulation suggests another potential application. If one knew the phytoplankton bioconcentration factor (BCF) for several metals but not for a metal proposed to be introduced into an aquatic system, a QICAR model could be produced from known information to predict a BCF for the metal of concern. In doing so, speciation calculations based on metal-ligand binding theory would likely improve the accuracy of predictions. Work with bioaccumulation of alkaline earth (Jeffree, 1988) and other metals (Markich et al., 2001) in Australian mussels suggests that this approach to predicting trends in metal bioaccumulation might also be possible with larger species.

Application in effect assessment would be similar to current uses of QSAR models for organic toxicants. Modeled trends based on effects known for a set of metals could be used to predict effect for a metal of interest for which no-effect aquatic toxicity data exist. Newman et al. (1998) conducted cross-validation calculations of diverse QICAR models and found acceptable prediction error for most.

HSAB theory provides an effective organizing theme for metal speciation, bioaccumulation, and effects. Existing information allows speciation and phase association prediction for exposure assessment—for example, the frequent application of the MINTEQ model. Potentially, bioaccumulation could be estimated for untested metals using data for other metals and HSAB-related metrics. Evidence is accumulating that suggests metal effects can be predicted for single metals and mixtures on the basis of the QICAR approach.

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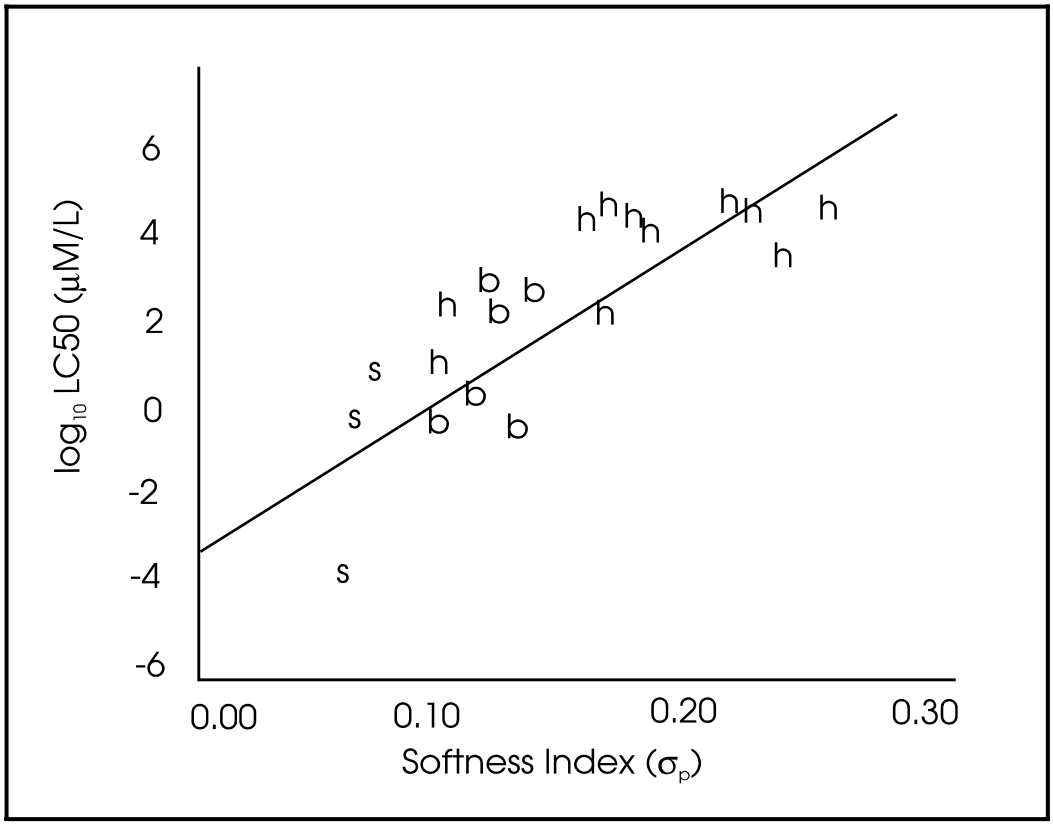

Figure 4. A QICAR model for log of LC50 (expressed as the predicted free ion concentration) using the softness index, F_p, as the predictive variable. Metal ions differed in charge and ranged from soft ("s": Ag, Cd, Hg), to borderline ("b": Co, Cu, Mn, Ni, Pb, Zn), to hard ("h": Ba, Ca, Cr, Cs, Fe, La, Li, Mg, Na, Sr) metal ions. Ninety-three percent of the variation in log LC50 (Microtox bioluminescence assay) could be explained by the model. Because these cations vary in several ways, a bivariate model including P_m^2r and Z^2/r provided the best model. That bivariate model accounted for 99% of the variation in log LC50.

Source: Adapted from McCloskey et al. (1996).

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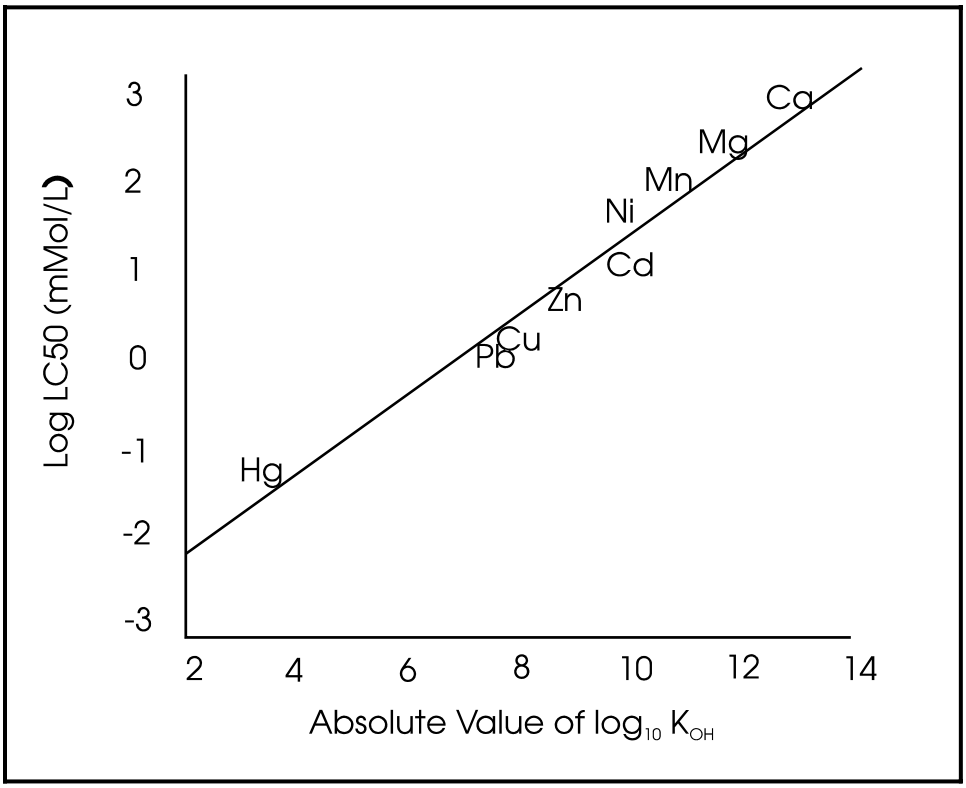

Figure 5. Prediction of LC_{50} for *C. elegans* exposed to divalent metals using the explanatory metric, $|\log K_{OH}|$.

Source: Adapted from Tatara et al. (1997).

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3.1.2.3. Limitations of HSAB to Metal Effects

The QICAR approach is best applied with a full understanding of the system under study. Newman et al. (1998) identified some systems in which free metal concentrations were the best metric of available metal concentration but calculation of speciation was not possible from the published information. Such a situation can diminish the effectiveness of predictions from metal-ligand binding theory-based models. Newman and McCloskey (1996) and McCloskey et al. (1996) found that the FIAM-based assumption that the free ion was the most bioavailable form of mercury was not sufficient to build the best QICAR model for the Microtox toxicity assay. Drawing on the studies of Simkiss (1983), Newman and McCloskey improved QICAR models including mercury by adding the neutral chloro-complex of Hg^{2+} to the estimated free Hg^{2+} concentration. The neutral chloro-complex ($HgCl_2^0$) is lipid soluble and must also be considered as bioavailable. Tatara et al. (1998) also found that consideration of specific interaction with excitable tissues was important to consider in constructing complete QICAR models for nematode toxicity. Suboptimal predictions occur in the absence of adequate understanding of the biology of the metals being modeled.

3.1.3. TRANSFORMATION OF METALS

3.1.3.1. Organo-metals/Metalloids Transformation Processes

Metals/metalloids can exist in the environment in several valence forms and as organometallic compounds. **Organometallic compounds** (referred to in this section collectively as **organometallics**) are compounds that have a metal/metalloid-carbon bond. Metal/metalloid transformation processes, such as metal methylation, occur through interactions with other chemicals and biota in the environment. Cycling and distribution of organometallic compounds between terrestrial, water, and atmospheric phases may be physically, chemically, or biologically mediated. Examples of some commonly occurring environmentally stable organometallic compounds are shown below.

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Metal/Metalloid	Stable Organometallic Compound
Arsenic	Methylarsenic acid, dimethyl arsenic acid, trimethyl arsine, trimethylarsine oxide
Lead	Tetramethyl/ethyl lead, trimethyl/ethyl lead, dimethyl/ethyl lead
Mercury	Methyl mercury, dimethyl mercury
Selenium	Dimethyl selenide, dimethyl diselenide, seleno-amino acids
Tin	Tributyltin, bis(tributlytin) oxide

Environmental methyl-metal concentrations reflect the net methylation rather than simple rates of methyl-metal synthesis. Metal methylation and demethylation rates in ecosystems are influenced by the speciation and biochemical availability of the metal. Metals involved in abiotic or biotic methylation/demethylation processes are presented in Table 3. With the exception of arsenic and selenium, the metals listed in the table form stable complexes with either methyl or ethyl groups. In addition to methyl/ethyl compounds, stable organometallic compounds such as lipids and arsenic and amino acids and selenium are incorporated biochemically.

Organometallic environmental transformations may affect both the mobility and the toxicity of these metals. *The rates of transformation and the organometallic products are dependent on environmental conditions and the population of microorganisms available.* For example, methylation/demethylation rates are dependent on the speciation of the metal, the microbial community, the environmental variables (e.g., pH, temperature, reduction oxidation potential, organic matter, dissolved oxygen, nutrient availability, salinity, complexing agents) and the distribution of the metal between compartments (sediment, water, gaseous). The inter-relatedness of these processes has made research into unraveling the factors controlling net methylation difficult and, to date, incomplete. However, some general trends can be predicted with some certainty, and these are discussed in this section.

3.1.3.1.1. Abiotic transformations

Organometallic compounds that are composed of metals with electronegatives >1.7 are the most stable under environmental conditions. Carbon-metal bonds with more polar (metal electronegatives <1.7) bonds will undergo hydrolysis (reaction with water). **Abiotic chemical**

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methylation can occur by three mechanisms: transmethylation reactions between mercury and tin/lead alkyls, humic/fulvic substances, and photochemical reactions. An example of an environmentally relevant abiotic transalklylation reaction is the organotin and mercuric chloride reaction shown below:

$$(CH_3)_3SnCl + HgCl_2 \rightarrow (CH_3)_2SnCl_2 + CH_3HgCl$$

Abiotic demethylation can occur by hydrolysis, photolysis, and oxidation. Abiotic demethylation of stable organometallic compounds is thought to be of minor importance unless the organic group is especially susceptible to the degradation mechanism.

Table 3. Metals/Metalloids Involved in Methylation Processes

Process	Metals affected
Environmentally stable organometallics	Si, Ge, Sn, Pb, Hg, As, Sb, Se
Abiotic chemical methylation	Hg, Pb, Sn
Abiotic demethylation	Sn, Pb
Biotic methylation	As, Cd, Hg, Pb, Se, Sn, (others? Sb, Pt,)
Biotic demethylation	As, Hg, Sn, Pb

Source: Bodek et al. (1988)

3.1.3.1.2. Biotic Methylation Transformations

Biotic methylation occurs when organisms, primarily microorganisms, transfer alkyl groups to bioavailable metals. In general, it is thought that anaerobic sulfate-reducing bacteria are the principal methylators in freshwater and estuarine environments. However, methylation rates are not always correlated with sulfate-reducing bacteria. Not all sulfate-reducing bacteria are capable of methylating, and efficiency of methylation is dependent on the activity and structure of the bacterial community. Other bacteria may be involved in methylation. In addition, nutrient availability, sulfate concentration and other environmental variables affect

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biotic methylation rates. The principal naturally occurring methylating agents found within organisms are methycobaliam (a form of vitamin B_{12}) and S-adenosyl methionine. Biotic methylation occurs predominantly in the sediment column; however, because the water column by volume is much larger, water column methylation is important.

Maximum methylation rates typically occur at the redox boundary, which varies seasonally and frequently coincides with the sediment-water interface (Ullrich et al., 2001). Methylation rates decrease with increasing sediment depth, probably due to a decrease in biotic habitat. Microorganisms may also demethylate (or dealkylate) organometallic compounds. Microbial-mediated transformations are frequently the most important environmental organometallic processes. Generally, as the amount of organic material increases in a system the microbial populations also increases. Examples of typical bacterial populations in natural waters and sediments are shown below (Ullrich et al., 2001).

3.1.3.1.2.1. *General environmental factors affecting methylation*. Formation of methyl-metals in ecosystems is influenced by numerous environmental variables. General trends of several notable parameters affecting methylation/demethylation rates are listed in Table 4; however, it

Environment	Bacteria numbers (1/mL)
Clear mountain lake	50–300
Turbid, nutrient rich lake	2000–12,000
Lake sediments	8,000,000,000–50,000,000,000
Stream sediments	0,000,000–100,000,000

should be noted that these trends are the best estimates of current data and many are poorly understood. Trends for all metals/metalloids are typically not available. If a trend is indicated in the table, data are generally known for at least two or three metals, for example, Hg and As or Hg, As, and Se.

High temperatures and anaerobic conditions generally favor metal-methylation formation, and demethylation processes are generally favored under low temperatures and/or

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aerobic conditions. Studies on the effects of pH are not consistent. Interconnected parameters include pH effects on the microbial communities and effects on the speciation distribution of the metals/metalloids in the water and the sediment as well as adsorption rates. Organometallic compounds appear to increase in the water column in low pH environments, but this may be due to release of methylated metals from the soil and subsequent depletion of organometallic compounds in the soil. Therefore, pH effects on net methylation in a system are not fully understood. In freshwater ecosystems, where sulfate concentrations are typically low, increase in sulfate concentration increases methylation rates. However, in reducing environments, increasing sulfide concentration decreases methylation rates.

The inhibitory effect of sulfide is probably not due to metal sulfide formation, but rather to the formation of less bioavailably charged metal-sulfur complexes. High organic matter may increase abiotic methylation through humic/fulvic metal reactions; however, this mechanism is poorly understood and confounded because biotic methylation rates may increase in environments with high organic matter. In ecosystems with high dissolved organic carbon (DOC) concentration, DOC may bind with metals/metalloids, rendering them unbioavailable and thereby reducing biotic methylation rates. The role of organic matter (DOC) on methylation rates is not well understood.

3.1.3.2. Atmospheric Transformations

3.1.3.2.1. Abiotic Chemical Methylation/Demethylation Transformations

Boiling points for organometallics for a given metal/metalloid decrease with increasing alkyl substitution and with shorter alkyl chains. For example, the boiling points of organotin compounds decrease, with dimethyltin dichloride > trimethyltin > tetramethyltin. Fully methylated metals such as dimethyl mercury may be transported great distances in the atmosphere due to the combined low boiling point and low water solubility. Methylation of Se, Hg, Pb, and As volatilizes these compounds, contributing to their air concentrations.

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Demethylation of organometallic compounds in the atmosphere occurs by primarily by photolysis, such as:

$$(CH_3)_2Hg(g) \xrightarrow{light} Hg^0 + 2CH_3$$

Demethylation may also occur by reaction with ozone, hydroxyl radicals, nitrate radicals, and sorption to particulate matter. Organometallic compounds are also removed from the atmosphere by wet/dry deposition.

Table 4. General Trends of Environmental Factors Affecting Rates of Methylation/Demethylation

Organometallic transformations	Temperature		pH		SO_4^{2-}	Organic matter	Redox		Salinity
	High	Low	High	Low	High		Oxic	Anoxic	High
Net methylation	↑	↓	?	?	?	?	↓	↑	↓
Methlyation aq	↑	↓	↓?	↑?	↓	↓↑	↓	↑	↓
Methylation sed	↑	?	↑	↓	↓	?	?	?	?
Demethylation	↓	↑	↓	↑	?	?	↑	↓	?

↑ indicates an increase in rate
↓ indicates a decrease in rate
? indicates conflicting data or insufficient data to indicate a likely trend

3.1.3.3. Aquatic Transformations

3.1.3.3.1. Abiotic Chemical Methylation/Demethylation Transformations

In stratified aquatic systems, methyl-metal/metalloid formation occurs predominantly at the oxic/anoxic interface. Organosiloxanes and other silicone-related substances have been considered as possible abiotic methylating agents. *Overall, abiotic methylation is probably of minor importance except in ecosystems with high organic matter*. The abiotic methylation of

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mercury with soluble humic substances (humic and fulvic acids) occurs under both aerobic and anaerobic conditions and appears to be enhanced by light and inhibited by chloride ions (ADSDR, 2003). Organolead compounds are decomposed by hydrolysis and photolysis. Abiotic degradation proceeds from trialkyl lead to dialkyl lead to inorganic lead. Abiotic demethylation processes for organotin are not well understood, but probably involve progressive debutylation; however, abiotic demethylation is thought to be less important then biotic demethylation processes for organotin compounds.

3.1.3.3.2. Biotic Methylation/Demethylation Transformations

Microbial methylation processes play the major role in methylation of Hg, Sn, As, with methycobalamin the most likely environmental methyl donor. Metal speciation is a prime factor regulating the methylation potential in a system. Until recently, Hg^{2+} was considered the main mercury species methylated by bacteria; however, current research indicates that uncharged Hg complexes are more likely the principal species methylated (Ullrich et al., 2001). Arsenate can be reductively methylated (via arsenite) under anoxic conditions to dimethylarsine. Selenium and selenite can be methylated via microorganisms; demethylation of organoselenium via other biotic processes is also known. The volatile compound tetramethyl lead is formed by microorganisms in anaerobic lake sediments, whereas aerobic sediments tetramethyl lead will be oxidized. *Methylation (biotic or abiotic) of lead is thought to be small compared to anthropogenic releases of organolead compounds* (Wade et al., 1993). Organolead can also be demethylated by microbial processes. The methylation of tin by methycobalamin requires the oxidation of Sn^{2+} to a Sn^{3+} radical, which can take place in the presence of Fe^{3+}. Biotic demethylation of organotin is thought to go through hydroxilated intermediates via stepwise debutylation, under both aerobic and anaerobic conditions.

3.1.3.3.3. Environmental Factors Affecting Methylation

Seasonal variation of methylated mercury is thought to be related to temperature, redox potential, and productivity. Seasonal variation for organic arsenic (dimethylarsenic) has also

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been reported, with organoarsenic species decreasing in late fall and winter. High seasonal concentrations of organoarsenic compounds have been postulated to be linked with algal blooms. Higher environmental temperatures promote methylation, whereas low temperatures promote demethylation. The effects of pH are complex: acidified lakewaters leads to increased methylation in the water column and decreased methylation in sediments. The reduction of methylation rates in the sediments may be due to reduction in the activity of sulfate-reducing bacteria or increased demethylation rates (Ullrich et al., 2001). In natural freshwaters, additional sulfate stimulates sulfate-reducing bacteria, which are important methylators of mercury in anaerobic sediments. However, when conditions favor sulfide formation (e.g., reducing conditions), inhibition of methylation rates is observed.

3.1.3.3.4. Examples of Organometallic Distribution

Distribution of organomercury in estuarine and marine waters as methylmercury is less than 5% of the total mercury, whereas in freshwaters methylmercury may be 10–30% of the total mercury, although normally it is on the order of 1–2%. Methylmercury concentrations in sediments are typically less than 1% of the total mercury, and they are lower still in estuarine and marine environments. Methylmercury is effectively taken up by aquatic biota and bioconcentrated. In top predator fish, most mercury (>95%) is methylmercury. Risk assessment methods and current research issues are discussed in U.S. EPA (1997, 2000).

Monomethylarsonic acid and dimethylarsinic acid are the two dominant organometallic arsenic compounds found in dissolved waters. Organic arsenic may account for 20% of the total arsenic in aquatic aerobic conditions, although organic arsenic in freshwater lakes has been reported to range from 1 to 59% of the total arsenic concentration (ATSDR, 2003). Dimethylarsenic is typically the dominant organic species. Reports of organic-arsenic (di- and trimethylated) range from 60 to 99% of the total arsenic in fish. Organic-arsenic accounts for 80% of total arsenic in shellfish. Algae and freshwater invertebrates uptake organoarsenic compounds; however, arsenic biomagnification in the aquatic food chain is not thought to be significant.

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Although plants, bacteria, and fungi have been demonstrated to synthesize selenoamino acids from inorganic selenium compounds, organoselenium compounds are not found in significant dissolved concentrations in water, probably due bacteria catabolizing the amino acids. In sediments from compromised ecosystems (e.g., Kesterson National Wildlife Refuge), 50% of the total selenium in the sediments can be organoselenium. The high organoselenium in these ecosystems has been attributed to plant decay settling to the sediment surface.

3.1.3.4. Terrestrial Transformations

3.1.3.4.1. Abiotic Chemical Methylation/Demethylation Transformations

Methylation and demethylation of organic mercury compounds in soils appear to be mediated by the same types of abiotic and microbial processes that occur in aquatic systems. The frequency and magnitude of soil moisture play an important role in availability and transformation processes. Because soils are primarily oxygenated systems, particularly in the root zone, conditions favorable to sulfide formation and bacterial methylation occur infrequently. With the exception of peat bogs and similar anoxic, highly saturated soils, methylation generally occurs only at very low rates in soils.

3.1.3.4.2. Biotic Methylation/Demethylation Transformations

Plants have the capacity to transform metals and metalloids that are taken up from the soil. The most notable example is selenium. Soluble inorganic oxanions of selenium are readily taken up by plants and converted to organoselenium compounds such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide. Demethylation/dealkylation of organoselenium (e.g., trimethylselenonium), organomercury, organoarsenic, and organotin can occur in soil.

3.1.3.4.3. Environmental Factors Affecting Methylation

Formation and degradation of organometallic compounds in soils appears to be mediated by many of the same types of microbial and environmental processes as in aquatic systems.

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Speciation of metals/metalloids dominates the methylation and/or uptake. Methylation/demethylation rates are affected by soil moisture: low moisture decreases biotic processes in soils. Soils high in iron and aluminum oxide, silts, and clay minerals interfere with methylation of metals/metalloids due to the reduced bioavailability of metals/metalloids. Plants methylate selenium, predominantly to selemethionine and some selenocysteine. Plant uptake and methylation of selenium or arsenic is specific to plant species. Many soil organisms are capable of converting arsenate/arsenite to volatile methylated arsines. Losses of 15–30% per year due to volatilization of arsenic in soil have been reported (ATSDR, 2003). Organolead complexes, on the other hand, are thought to be relatively stable in soils.

3.1.3.5. Organometallic Transformation: Summary

Organometallic methylation and demethylation rates are influenced by both speciation and bioavailability of the metal, the microbial community, and a large number of environmental factors, many of which are interrelated. Sulfide and organic matter are important environmental variables that significantly affect methylation and are as yet poorly understood. Which variables dominate differs among locations and between seasons, although it is clear that methylation is predominantly a biotic-mediated process. Methylation/demethylation rates are strongly influenced by the metal/metalloid speciation and bioavailability.

3.1.4. AQUATIC CHEMISTRY

3.1.4.1. Speciation

For many metals, it is believed that the free ion is the primary metal species that causes toxicity to aquatic organisms. Accordingly, the key parameters that can modify the degree of toxicity are those that affect speciation, such as pH and the amount of inorganic and organic ligands (e.g., DOC) that provide alternative binding sites for the metal ion. In addition, metal toxicity is also affected by other dissolved ions (e.g., Na, Ca) that compete with metals for binding sites on the gills or other respiratory surfaces of aquatic organisms.

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Metal species dissolved in water can be described as free ions or aquo-complexes, or simply as "complexes." A complex is a dissolved species that exists because of the association of a cation with an anion or neutral molecule (Langmuir, 1997). A ligand is an anion or neutral molecule that can combine with a cation (such as the free metal ion) to form a complex. The total analytical concentration of a given metal in water is the sum of the concentrations of its free ion and its complexes and any metal associated with suspended solids, whether organic or mineral. For example, the total molal concentration of lead, ΣPb, in a natural water might equal

$$\Sigma Pb = mPb^{2+} + mPbOH^{+} + mPbCO_3^{o} + mPbHCO_3^{+} + mPbSO_4^{o} + mPb(\text{suspended solids})$$

In most natural waters the concentration of free lead ion, mPb^{2+}, is less than the sum of the concentrations of its complexes, which in this case are lead complexes with hydroxyl, carbonate, bicarbonate, and sulfate ions. Other metals that are found in natural waters most often as complexes and not as free ions include Al^{3+}, Ag^{+}, Cu^{2+}, Fe^{3+}, and Hg^{2+}. The metalloids As and Se and the metals Cr, Mo, Sb, and V occur most often in aerobic waters and soils as covalently bonded to oxygen in oxyanions. Under oxidizing conditions these include arsenate, selenate, chromate, molybdate, and vanadate, which themselves are complexes.

Complexes that incorporate metals play a major role in controlling the availability and fate of metals in the environment. Increasing the fraction of a metal that is complexed increases the solubility of minerals of that metal (Langmuir, 1997). For example, the solubility of lead sulfate is related to the molal concentrations of free lead and sulfate ions through the expression:

$$K_{sp} = [(\gamma_{Pb}.mPb^{2+})(\gamma_{SO4}.mSO_4^{2-})]$$

where the terms γ_{Pb} and γ_{SO4} are the activity coefficients of the ions. The product of the ion activity coefficient and the molal concentration of each species equals the activity of the ion. The second equation shows that the activity of free lead ion controls the solubility of lead sulfate. For a given total lead concentration (see the first equation), the more of the lead that is complexed, the lower will be the concentration of free lead ion. This means that as the extent of lead

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complexing increases, the total lead concentration must also increase in order to reach saturation with lead sulfate. In other words, metal complexing increases total metal solubility.

Metal complexing also has a direct influence on metal adsorption to organic matter or mineral surfaces. For example, metal carbonate, sulfate, and fluoride complexes are usually poorly adsorbed, whereas metal hydroxide complexes are strongly adsorbed (Langmuir, 1997). In summary, metal complexing generally increases the solubility and mobility of metals in surface and ground waters.

3.1.4.2. Effects Concentration and Bioavailability

The traditional method of predicting effects of metals on aquatic organisms is to estimate an effects concentration for the water column and the sediment. For the water column, the EPA's WQC (Stephen et al., 1985, U.S. EPA 1986, 1996) or the Predicted No Effect Concentration derived following the European Union's (EU's) technical guidelines (EU, 1996) are frequently used as default screening values. However, these criteria make only limited corrections for bioavailability, taking into account only water hardness and ignoring other modifying factors such as pH and competing ligands. The BLM was developed to remedy this situation (U.S. EPA, 1999, 2000; Di Toro et al., 2000; Paquin et al., 2002__). It incorporates the WHAM speciation model and it also models the competitive metal binding at the toxic site of action (the biotic ligand). BLMs are currently available for copper and silver (Di Toro et al., 2000; Santore et al., 2000) and zinc (Santore et al., 2002) and are under development for cadmium, nickel, and lead (U.S. EPA, 20XX). The development and use of the BLM is covered in detail in Section 3.4. Ecological Effects.

3.1.5. Ground Water and Metals Mobility

Site-specific risk assessments for all EPA programs need to be able to predict the rate of movement of metals through soils and their subsequent movement and concentrations in ground water. For example, metals criteria for the toxicity characteristic in RCRA depend on the development of a generic soil-to-ground water dilution attenuation factor (55 Fed. Reg. 61,

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11798 (March, 29, 1990**))**. The primary processes governing the environmental fate and transport of metals in the subsurface are advection, dispersion, matrix diffusion, and retardation (U.S. EPA, 1994). Advection and dispersion are functions of the system rather than of the contaminant. Matrix diffusion, which is a function of the contaminant, is relatively unimportant and is omitted in most model transport algorithms. Retardation depends on a number of factors (U.S. EPA, 1994; Langmuir, 1997a) and may involve or be affected by the following:

1. Sorption: the attachment of chemical species to mineral surfaces or other surfaces.

2. Ion exchange: competitive adsorption of ionic species, including ionic contaminants and major ions, onto oppositely charged surfaces of geologic materials.

3. Speciation: the distribution of a given constituent among its possible chemical forms, including metal complexes, which have differing tendencies to be adsorbed or desorbed.

4. Precipitation: the process by which dissolved species exceed the solubility limits of their solids, so that some of the species precipitate from solution. When a metal species reaches mineral saturation, addition of further amounts of the species to solution are precipitated, not adsorbed.

5. Colloid formation: the process of forming colloids and the association of metal species with them. The metals may be sorbed or coprecipitated with colloidal-sized particles.

6. Biofixation: the binding of metals to solid materials due to the interactions of microorganisms or plants.

7. Natural organic matter (NOM) interactions.

8. Anion exclusion: negatively charged mineral or other surfaces repelling anions and so preventing their sorption by those surfaces.

9. Other important processes: changes in pH, oxidation potential, salinity, concentrations of competing ions, the nature of sorbent phases and their surface areas, and surface site densities.

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3.1.5.1. Application of Partition Coefficients to Metal Mobility in Ground Water

Due to the complexity and multiplicity of the processes involved, recourse is often made to the use of a single partition or distribution coefficient that describes the degree to which the contaminant's transport is retarded relative to water. This approach starts with defining the retardation factor:

$$R_f = \frac{v_p}{v_c}$$

where R_f is the retardation factor, ν_p the velocity of water through a control volume, and ν_c the velocity of contaminant through a control volume. The retardation factor is related to the distribution coefficient through the expression:

$$R_f = 1 + \frac{\rho_b}{n_e} K_d$$

where: ρ_b is the porous media bulk density; and
n_e is the effective porosity at saturation given as a volume fraction
(Langmuir, 1997a).

Laboratory adsorption studies often find that, in simple systems, the value of log K_d for metal adsorption increases linearly with pH. For example, for Zn^{2+} adsorption by ferric oxyhydroxide (HFO), Langmuir (1997a) noted that adsorption followed the log equation:

$$K_d = -5.48 + 1.77\ pH$$

U.S. EPA (1999b) presents a comprehensive review of the properties and applications of partition or distribution coefficients for metals. These coefficients may be obtained from the literature, estimated using mathematical models, or measured. Partition coefficients tabulated as a function of pH by EPA (U.S. EPA, 1998) are listed in Table 5 for several important elements of potential concern. EPA (U.S. EPA, 1999b) has also presented non-pH-dependent values for lead

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(900), mercuric chloride (58,000), and elemental mercury (1,000), which for reasons just discussed should be used with considerable caution.

It has been observed that in many soils and sediments low in organic matter, HFO is the most important metal sorbent and the only sorbent that needs to be considered in predictions of toxic metal sorption behavior (Benjamin and Leckie, 1981). The diffuse layer (DL) model (also called the generalized two-layer model, or GTLM) in MINTEQA2 has been extensively applied in aquatic environmental studies of metal transport and attenuation. Loux et al. (1989) used the DL model and MINTEQA2 to predict the adsorption and precipitation behavior of eight metals in an oxidized, sandy aquifer as a function of pH. Assuming that HFO was the only sorbent, DL model adsorption adequately described changes in the concentrations of Ni, Pb, and Zn in the sediment. Cadmium behavior was better understood, assuming its precipitation in $CdCO_3$ (otavite). Changes in Cu, Ba, Be, and Tl were not simply explained. Copper may have been adsorbed by organic matter, which was not considered in the modeling.

More recently, adsorption of metals by organic matter and aluminum oxyhydroxies as well as HFO has been included in DL modeling with MINTEQA2 (Paulson and Balistieri, 1999). These authors studied neutralization of acidic ground waters by ambient surface and ground waters using a mixing model approach. Particulate organic matter (POC) and HFO were the chief metal sorbents. In pristine systems, Cu is usually the chief metal associated with POC; in the Paulson and Balistieri study, Zn and Cd were mostly adsorbed by POC, and Cu was mostly absorbed by HFO.

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Table 5. Partition Coefficients as a Function of pH for Several Important Elements of Potential Concern

Element	pH 4.9	pH 6.8	pH 8
Arsenic (V)	25	29	31
Barium	11	41	52
Beryllium	23	790	100,000
Cadmium	15	73	4,300
Chromium (III)	1,200	1,800,000	4,300,000
Chromium (VI)	31	19	14
Lead (need values)			
Nickel	16	65	1,900
Selenium (VI)	18	5	2.2
Silver	0.1	8.3	110
Thallium (I)	44	71	96
Zinc		62	

Source: U.S. EPA (1998)

It may be possible to estimate metal adsorption with some accuracy without having to measure it, depending on the information available on a specific soil, surface water, or ground water system. What is needed minimally is the amount of potentially sorbing materials (e.g., metal oxides, clays, and organic matter) in a soil or sediment or in suspension in a stream. Literature information can then be used to estimate the sorption properties of these materials for use in a sorption model. For example, as noted above in the discussion of the DL adsorption model, where HFO is the dominant sorbent and the amount suspended in a stream is known, estimation of metal adsorption can be accurate to within 10–20%, as shown in Table 6 (Smith et al., 1998). As a general observation, other things being equal, it has be found that the surface charge density—and thus the metal adsorption capacity—of most minerals is largely a function of their surface areas exposed to water (Pabalan et al., 1998). Thus, the adsorption of metals by Al and Fe (III) oxyhydroxides in a system at a given pH may be assumed to be the same if they have the same surface areas.

Cederberg et al. (1985) and Yeh and Tripathi (1991) considered surface complexation modeling of metal adsorption and metal transport in ground water. Parkhurst (2002) developed a

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computer model called PHAST,[3] which is a 3D reactive transport model that combines PHREEQC, which has the DL metal adsorption model, with HST3D, a ground water flow and transport model.

Table 6. Comparison of Model Predictions[a] and Measured Values of Percent Metals Associated With the Suspended Particulate Fraction of Mine Drainage Waters From Select Sites

	Argo-3 (pH 5.6, HFO = 0.007 g/L)		Rawley-3 (pH 6.2, HFO = 0.11 g/L)		Leadville Drain (pH 7.2, HFO = 0.001 g/L)	
Metal	**Predicted**	**Measured**	**Predicted**	**Measured**	**Predicted**	**Measured**
As	–	–	98	<78[b]	–	–
Pb	82	<71[b]	80	<93[b]	86	<71[b]
Cu	18	27	60	63	–	–
Zn	<1	0 to 8	<1	0 to 9	2	3
Ni	<1	<1	<1	1	–	–
Cd	<1	<1	<1	6	<1	<1

[a]Model predictions made with the diffuse layer model and MINTEQA2. (Source: Smith et al., 1998)
[b]Dissolved concentration was below the detection limit; value was computed using the limit of detection for the dissolved concentration.

The distribution coefficient approach can provide accurate modeling results for organic contaminants, but it is likely to be in serious error when applied to the transport of metals through porous media at specific sites.

The application of single partition coefficient values for individual metals should be limited to regional and national scale studies where accuracy is not required and bounding or representative values are adequate.

Several recent studies have measured and modeled trace metal adsorption and metal transport in streams using a surface complexation approach to adsorption. U.S. Geological Survey researchers of the Toxic Substances Hydrology Program have published a number of papers using the OTEQ and OTIS models. OTEQ is a one-

[3] See http://wwwbrr.cr.usgs.gov/projects/GWC_coupled/.

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dimensional model for studying the fate and transport of metals in streams and rivers. The model couples the OTIS transient storage model with MINTEQ, which includes DL model adsorption of metals by HFO (Ball et al., 1999; Runkel et al., 1999). Runkel et al. (1999) considered in-stream metal transport, metal oxide precipitation-dissolution, and pH-dependent sorption of copper and zinc.

If greater accuracy or site specificity is required, it may be necessary to measure metal adsorption in laboratory experiments. Such measurements can be performed on pure minerals or on whole (usually sieved) soils. The sorption results may be used to develop DL model parameters for metal adsorption (Dzombak and Morel, 1990; Stumm, 1992). Model results may then be used to compute partition or distribution coefficients as a function of pH, for example.

Several chemical mass transport codes are available that can model metal transport through porous media using the more accurate DL adsorption model for metals. These models include PHREEQC (Parkhurst and Appelo, 1999) and CHMTRNS (Noorishad et al., 1987) and, for transport by streams, OTIS/OTEQ (Runkel et al., 1999). Even if model parameters are estimated on the basis of literature values, such models will generally predict metal adsorption and retardation more accurately than is possible when using single or linearly varying distribution coefficient values.

3.1.5.1.1. Limitations

The DL and MINTEQA2 models (Smith et al., 1998) apply only if fluid flow in the porous media (soil or sediment) is isotropic and adsorption is fast, reversible, and linear (Freeze and Cherry, 1979). These assumptions are often not valid, particularly for metal adsorption. As discussed above, the distribution coefficient approach can provide accurate modeling results for organic contaminants, but it is likely to be in serious error when applied to the transport of metals through porous media at specific sites. This is because, as emphasized previously, the reactions and processes that control metal sorption are far greater in number than is the case for the adsorption of organic substances. Some transport models assume a constant partition coefficient or linearity of the partition coefficient over all concentration ranges. To the extent that sorption is not constant and follows a nonlinear isotherm (which is the usual case for metals), these

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models will be inaccurate and should be avoided. The best that can be hoped for when single partition coefficients are used to describe metal adsorption is that they represent bounding values in a given application.

3.1.5.1.2. Use in Decision Making

U.S. EPA (1999b) discusses the advantages and disadvantages of several methods for measuring partition coefficients, including laboratory batch testing, in situ field batch testing, flow-through testing, and field modeling. In many national assessments, EPA has used the MINTEQ model and its subsequent versions to generate generic partition coefficients that may be applied to regional or national mobility evaluations (http://www.epa.gov/ceampubl/mmedia/ minteq/index.htm or http://www.lwr.kth.se/english/ OurSoftware/Vminteq/).

As noted previously in the discussion of adsorption, metal partition coefficients can vary by several orders of magnitude over short distances (meters or less) in porous media because of changes not only in pH, but also in metal complex formation, metal adsorption competition, the solid:solution ratio, relative abundances, surface areas, and surface charge densities of the different metal-sorbing phases.

3.1.5.2. Monitored Natural Attenuation of Inorganic Contaminants in Ground Water, Including Metals, Metalloids, and Radionuclides: Framework for Decision Makers

Monitored natural attenuation (MNA) has been applied as a knowledge-based remediation technology for organic contaminants in ground water. The application of this technology is being considered for remediation of inorganic contaminants in ground water at waste sites. In order to provide regulators and the regulated community with the appropriate information for assessing the viability of this technology, EPA's Office of Research and Development (ORD) has initiated an effort to develop an Agency framework document to serve as a point of reference for evaluating MNA as a sole or partial remedy for ground water restoration at contaminated sites.

ORD is leading an effort, in cooperation with EPA's Office of Solid Waste and Emergency Response (OSWER) and Office of Air and Radiation, to develop the MNA

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framework document to provide the policy, scientific, and technical framework for assessing the viability of MNA for inorganic contaminants in ground water. Initial guidance on the application of MNA for all ground water contaminants was first provided by EPA through an OSWER Directive (U.S. EPA, 1999). The purpose of this Directive was to clarify EPA policy on the use of MNA for remediation of contaminated soil and ground water. However, this publication is limited in scope with respect to providing detailed requirements for the technical assessment of inorganic contaminant MNA at waste sites.

The behavior of inorganic contaminants in the subsurface differs significantly from that of organic contaminants in that microbial degradation is not a viable process for contaminant removal. The primary processes effective for natural attenuation of inorganic contaminants (radionuclides and nonradionuclides) are immobilization and radioactive decay. The assessment of contaminant immobilization requires establishing contaminant removal onto immobile aquifer solids and verification of the stability of the removal process toward remobilization due to changes in site geochemistry. This necessitates knowledge of the hydrologic and biogeochemical processes that control contaminant mobility in the subsurface.

3.1.5.2.1. Application/Limitations

The MNA framework document outlines the tasks to be accomplished as part of a site-specific assessment. These tasks are apportioned within a tiered process in which a progressively increasing level of knowledge is required to successfully demonstrate MNA viability. Candidate sites that do not meet the requirements of a given tier will be eliminated from consideration for application of MNA.

Site evaluation is performed within a four-tiered process designed to minimize site uncertainty as MNA-specific data are collected. Tier I analysis leads to elimination of sites inappropriate for MNA if any of the following criteria are not satisfied (U.S. EPA, 1999):

- The contaminant is not contributing to a direct human health threat;
- The source term is either limited or controlled;

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- The plume is static or retreating; or
- Direct geochemical measurements at the site indicate that contaminant(s) attenuation is occurring.

Tier II analysis establishes the attenuation capacity of a particular site and is used to eliminate the site from further consideration if the capacity does not exceed the estimated contaminant mass. Tier III analysis is used to establish the stability of the attenuation process(es) with respect to current and anticipated site geochemical conditions. Tier IV involves development of a long-term monitoring plan to track MNA performance and contingency remedial technologies that can be implemented in the event of MNA failure. The monitoring plan will include identification of geochemical triggers that serve to alert site managers to MNA failure. Requirements and techniques for acquisition of site-specific data for each tier will be outlined within the framework document.

The MNA framework document is divided into two major parts. The first part provides the policy, scientific basis, and framework for technical assessment of MNA for inorganic contaminants. Technical subjects that are discussed include (1) the scientific basis for contaminant immobilization and radioactive decay, (2) requirements and approaches for site characterization to define site hydrology and biogeochemistry, and (3) the application of conceptual and mathematical models within the tiered process. The second part provides element-specific assessments of MNA feasibility based on the current state of knowledge. Radioactive and nonradioactive contaminants covered within this part of the MNA framework document are listed below:

Radioactive contaminants	**Nonradioactive contaminants**
Americium, cesium, cobalt, iodine, plutonium, radium, radon, strontium, technetium, thorium, tritium, uranium	Arsenic, cadmium, chromium, copper, lead, mercury, nickel, nitrate, perchlorate, selenium, zinc

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Athough this list does not address all potential contaminants, it represents a comprehensive range of contaminant geochemistry and viability for MNA. Element-specific assessments will provide the basis for identifying whether a particular contaminant falls within the general categories of nonviable, limited viability, or viable. This information provides the end user with a tool to screen candidate sites early on in the assessment process in order to minimize costs incurred with application of MNA. The framework document is scheduled for publication during Fiscal Year 2005 following internal and external peer review.

3.1.6. SEDIMENT CHEMISTRY

In addition to the challenges posed by metal chemistry, the sedimentary environment is complex and often highly heterogenous. Fortunately, we can draw generalizations about the sedimentary environment and the main controlling factors in order to progress towards a method for risk assessment. This brief review summarizes information on the composition of sediments, processes that act on sediments and their metal burden, and the chemistry of the sedimentary environment that influences the fate, bioavailability, and effects of metals. It is important to consider these factors in light of the aim of estimating potential biological effects of metals in sediments.

The solid phase of sediments can hold up to a million times more metal than can an equivalent volume of water. The exact proportions of a chemical held by sediment relative to water is a function of a metal's chemistry as well as the chemistry of the sediment solid and the surrounding environment, and this distribution is dynamic (Diamond and Mudroch, 1990). Because of their large capacity to "hold" metals, sediments have been characterized as "sinks." Although this is largely true, sediments are now appreciated to be temporary sinks, wherein some of the metal can enter ecological and human food webs through several routes (e.g., Diamond, 1995), primarily through accumulation in benthic organisms. These organisms include those that fully or partially live in the sediments (e.g., tubificids, chironomids, trichopteran larvae) or those that feed from the sediment bed (e.g., suckers, carp). Some organisms obtain their chemical dose from both pelagic and benthic routes (e.g., lake whitefish, walleye), but because of high chemical

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concentrations in sediments, the benthic route can be the dominant route of uptake (Morrison et al., 2000).

For humans, the route of entry of metals from the sediments is through water used for drinking, bathing, and swimming. The availability of these metals is mediated by sediment-water exchange processes that can result in the release or remobilization of chemicals from the sediment bed. However, due to the ability of Hg to bioaccumulate in its monomethyl form, fish consumption is the critical route of exposure to this metal for humans.[4]

Most sediment chemistry occurs with the fine-grained materials that accumulate in the deep parts of water bodies. The controlling factors or master variables that influence metal chemistry are redox potential and pH. A depth profile of the sediments will reveal decreasing sediment porosity and concentrations of dissolved oxygen because oxygen is consumed as organic matter decomposes. pH is often relatively constant or may decrease with depth, but alkalinity may increase due to mineralization of organic matter (Stumm and Morgan, 1996). As the dissolved oxygen is consumed, anaerobic microbes use other electron acceptors in redox or oxidation-reduction reactions in the order of nitrate, ferric iron, ammonium, sulphate, and bicarbonate to produce carbon dioxide, ammonium, phosphate, hydrosulphide, and methane (e.g., Stumm and Morgan, 1996).

> Bed or bottom sediments are found at the bottom of lakes, rivers, and estuaries. Sediments have several sources that influence their composition and chemistry. The type and chemistry of sediments is also determined by their location in the water body as well as the characteristics of the water body. At any given site, metals can be associated with solid-phase minerals, organic matter, colloids, and pore water. The solid phase can vary from sand (>63 :m), to silt (2–63 :m), to clay (<2 :m). Because clays have more active binding sites than do the other grain sizes and because of their high surface area-to-volume ratio, these fine-grained particles are of greatest significance in terms of metal binding. Controlling factors or master variables that influence metal chemistry are redox potential and pH.

The redox status of the sediments can be assessed by measuring, in the pore water, the concentration of dissolved oxygen or other redox-sensitive species; by calculating på, which is a

[4]Marine biota can also be a significant route of exposure to arsenic in its organic forms, such as methylarsonic acid; however, these arsenic species are significantly less toxic than the inorganic forms (Fowler, 1983).

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measure of the availability of electrons in solution; or by measuring Eh (millivolts) or the electromotive force of the pore water solution. The zone of transition from oxic to anoxic conditions is the redoxycline, which can migrate vertically, depending on the mixing of the overlying water column (e.g., Diamond 1990). For example, the redoxycline may be 5 to 10 cm below the sediment-water interface in a well-oxygenated oligotrophic lake or river, but it may be above the sediment-water interface in a thermally stratified eutrophic lake or river.

3.1.6.1. Metal Chemistry in Sediments

In this discussion, two pools of metals must be considered. The first pool is metals that exist as aqueous (or dissolved) species bound to colloids or dissolved organic matter (DOM) and those bound to sediment particles through an exchangeable binding process. This pool is often referred to as the exchangeable or labile pool. The second pool is metals that are found within the mineral matrix of the sediment solids. This pool is largely unavailable to biota, and its release will occur over geologic time scales through diagenetic processes. Because the latter pool is largely unavailable, we will consider only the exchangeable pool of metals. Note that the exchangeable pool will be composed of naturally occurring metals that are released into solution due to weathering and diagenetic processes as well as metals released into the environment due to anthropogenic activities.

The exchangeable pool of metals is subject to speciation in the aqueous phase (e.g., within the pore water) and sorption to solid phases, where sorption is a general term that includes adsorption (the accumulation of matter at the solid-water interface or a two-dimensional process) and absorption (inclusion in a three-dimensional matrix) (Stumm and Morgan, 1996). Here, speciation refers to the distribution of metal species in a particular sample or matrix or species distribution (Templeton et al., 2000). In the aqueous phase, metal will react or bind with dissolved ligands according to the pH, Eh, ionic strength, and abundance of ligands (see above discussion on aquatic chemistry).

The concentration of metal in the dissolved phase is controlled by sorption to the solid phase. Whereas sorption can occur rapidly, desorption or dissolution of metal from the solid phase may be a two-phase process, where the second phase is rate limiting (e.g., Nyffeler, 1986;

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Santschi et al., 1986). If we neglect the kinetic limitation of reactions, the distribution of metals among aqueous species and between the aqueous phase and the solid phase can be estimated, assuming thermodynamic equilibrium. Several speciation/complexation models are available to perform this calculation, for example, MINEQL+ (Schecher and McAvoy, 2001), the Windermere Humic Aqueous Model (WHAM) (Lofts and Tipping, 1998), and MINTEQA2 (Allison et al., 1987). These models work well under oxic conditions, but estimates of metal binding are less reliable under anoxic conditions, where metal solubility is usually controlled by sulphides. Furthermore, in some circumstances equilibrium may not be achieved, particularly when the redoxycline moves more quickly than the rate of metal reaction or when the reaction is governed by microbial processes, as occurs with the methylation of mercury or arsenic.

In oxic sediment pore waters (above the redoxycline), metals will exist as aqueous species, that is, as freely dissolved ions (most transition metals exist as mono- or divalent cations, whereas metalloids exist as hydroxy-anions), aqueous species with dissolved ligands (e.g., carbonate), and complexed with colloids. Solid-phase reactions are controlled by iron oxyhydroxides and manganese oxides that may exist as colloids, sediment particles or surface coatings of particles, organic matter that may also exist as colloids or coat sediment particles, and clay colloids and particles.

As Eh declines, the solid-phase manganese oxides are the first to be reduced and thereby dissolve, which releases metals complexed with this mineral. The metals released into the pore water will then complex with iron oxyhydroxides, which are the next to dissolve as the Eh continues to drop. Under reducing conditions, particularly as sulphate is consumed and the sulphur is converted to sulphide, metal concentrations in pore waters again drop as solid-phase metal-sulphide complexes are formed (see discussion below about the role of AVSs in regulating toxicity).

As a result of redox chemistry, metals can undergo seasonal redox-driven cycling between the water column and sediments or within the sediments, depending on the position of the redoxycline. The stages in the cycling are, first, the complexation of metals with iron and manganese hydroxides under oxidizing conditions; then movement of these complexes into moderately reducing conditions and the release of manganese, iron, and metals into the water or

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pore water; and then diffusion of the dissolved metal upwards toward the zone of low metal concentration under oxidizing conditions. It is also possible for dissolved metal to diffuse downward toward the zone of low metal concentration due to complexation with sulphides. As a result of this vertical cycling, the depth profile of metals in pore water may not match that of the solid phase (e.g., Carignan and Tessier, 1985). Moreover, it is possible, but less usual, that the cycling can occur relatively rapidly and involve a significant portion of the solid-phase metal. Under these conditions, the solid-phase sediment profile reflects this re-working rather than the historical record of metal loadings (MacDonald et al., 200X).

pH controls metal speciation and binding by affecting the species distribution of dissolved ligands (e.g., carbonate vs. bicarbonate, solubility of humic substances) and the surface charge of binding sites on DOM and solid phases such as iron oxyhydroxides. Generally, at low pH, when surface sites are protonated, the sorption of cationic metals decreases, and, hence, metal mobility increases. The converse occurs at high pH, which results in low metal solubility and greater sorption. The patterns of dissolution and sorption are reversed for metalloids, such as arsenic, that exist as acidic species.

3.1.6.2. Methods of Estimating Metal Distribution in Sediments

3.1.6.2.1. Application

A main objective in terms of assessing the hazard or risk posed by metals is estimating metal in the dissolved phase that is potentially bioavailable. Accordingly, several methods have been developed to estimate the distribution of metals among dissolved and solid phases in sediments. These methods have been thoroughly reviewed by Mudroch et al. (1997, 1999). Although bioavailability is also a function of aqueous phase speciation (see above discussions in Aquatic Chemistry section), limited research has been conducted to estimate metal speciation in pore waters. Generally, ecological risk assessments assume that the exposure of benthic organisms to sediment-associated metal is proportional to the metal concentrations in interstitial water, although some studies indicate that uptake from overlying water (Roy and Hare, 1999; Hare et al., 2003) or ingested sediment may be a significant source of body burdens of metals (see Section 3.2 on exposure for more discussion of this topic).

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Distribution of metals in sediment pore waters may be determined by field measurements, experimental methods, and mathematical modeling, with the latter also requiring some field measurements. Concentrations of metals in pore waters may be determined in the field by use of pore water dialysis chambers or peepers and by methods that separate the solid phase from the pore water, although the latter have been shown to be less reliable (Mudroch et al., 1997). Several extraction schemes have been developed to determine the distribution of metal among operationally defined fractions (e.g., Tessier et al., 1979; Forstner, 1995). Other experimental methods include leaching tests (e.g., Reuther, 1999). The results of any of these methods are concentrations of metals in pore water, which can be related to toxicity benchmarks.

Because of the need to develop sediment quality guidelines (SQGs) for metals that explicitly address toxicity and are based on readily measured parameters, several methods have been developed. For oxic sediments, Tessier and co-workers (Tessier, 1992; Tessier et al., 1984, 1989, 1993) compiled partition coefficients of metals that were derived from field studies of freshwater sediments. The partition coefficients are dependent on pH (because Eh is held constant) and are generally linear over a range of pore water pH values (see above discussion under ground water chemistry for the theoretical basis for development of partition coefficients). Speciation/complexation models may also be used to estimate fractions of dissolved and bound metal species. These models rely on measurements of pH, dissolved oxygen, or Eh to establish redox conditions and concentrations of dissolved ligands and sediment solids. The models assume that solid-phase binding is governed by sorption to iron and manganese oxides. Model estimates are less reliable when other solid-phase substrates are present (e.g., clay minerals) and are a function of the availability and accuracy of the stability constants for the metal-ligand reactions that are used in the calculations.

For anoxic sediments, the availability of sulphide controls metal distribution and solubility. Operationally, AVSs—mainly iron monosulphide—have been considered as a measure of reactive sulphides (Forstner, 1995). Studies have demonstrated an inverse relationship between sediment toxicity and AVSs for marine and freshwater sediments (Di Toro et al., 1990, 1992; Ankley et al., 1991) as well as between pore water concentrations and AVSs (Brumbaugh et al., 1994; Casas and Crecelius, 1994). As a screening-level tool, the toxicity of anoxic sediments can be assessed by determining the ratio of AVSs to simultaneously extracted metal (SEM). Low sediment toxicity is indicated when AVSs are in excess (AVS > SEM),

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which implies sufficient capacity of the AVS to bind essentially all free metal. This topic is further discussed in Section 3.4.

For estimating effects concentrations in the sediment, there are many different SQGs, which vary in their derivation and the degree to which they incorporate bioavailability considerations. Many of the published SQGs are based on empirical relationships between biological effects and the total (dry weight) concentrations of sediment contaminants (e.g., Long and Morgan, 1991; McDonald et al., 1996). Although these empirically based guidelines do show general relationships between the degree of sediment contamination, they do not explicitly account for site-specific differences in bioavailability of contaminants. Although EPA has not formally adopted any single SQG approach as an Agency standard, it has been active in developing the "equilibrium partitioning" (EqP) approach to SQG development. The EqP approach considers effects of sediment chemistry on bioavailability by comparing the concentrations of AVSs, SEM, and organic carbon (Di Toro et al., 1990, 1992; Ankley et al., 1993, 1996; U.S. EPA, 2000). This approach is reviewed in more detail in Section 3.4. Ecological Effects.

3.1.6.2.2. Limitations

Model estimates are less reliable when other solid-phase substrates are present (e.g., clay minerals), and they are a function of the availability and accuracy of the stability constants for the metal-ligand reactions that are used in the calculations.

3.1.7. SOIL CHEMISTRY[5]

Metals occur naturally in soils as amorphous oxides and hydroxides and to a lesser extent as carbonates, phosphates, sulfates, and sulfides, which are relatively insoluble. The soil parameters important in affecting sorption and precipitation reactions and the extent of their influence—and thus their contaminant bioavailability—are dependent on the intrinsic properties

[5]Portions of this section were taken from Chapter 2 of *Guidance for Developing Ecological Soil Screening Level*. OSWER Directive 92857-55. U.S. EPA, Office of Solid Waste and Emergency Response. Washington, DC. August, 2003.

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of the contaminants. Metals can exist as either cations or anions in the soil environment, which significantly affects their sorption, mobility, and solubility (Table 8). For example, soil is primarily negatively charged; thus, metal cations have a higher propensity to be sorbed by soil particles relative to metal anions.

As identified in Table 7, most metals typically exist as cationic species. These metals can complex with inorganic soil constituents (e.g., carbonates, sulfates, hydroxides, sulfides) to form either precipitates or positively charged complexes. Both complexation and precipitation reactions are pH dependent. Therefore, although these metals can form complexes with a net negative charge, under most environmentally relevant scenarios (pH = 4 to 8.5), these metals either precipitate or exist as cations.

Arsenic, chromium, selenium, and vanadium complex with oxygen and typically exist as anionic species under most environmentally relevant scenarios (Bohn et al., 1985; Lindsay, 1979). The most common forms of arsenic are arsenate (arsenic V) and arsenite (arsenic III), which are present in soil solution in the form of AsO_4^{3-} and AsO^{2-}, respectively. The chemistry of arsenic resembles that of phosphate (Barber, 1995; Bohn et al., 1985). Chromium can exist as chromate (chromium VI or CrO_4^{2-}), which is usually considered more soluble, mobile, and bioavailable than the sparingly soluble chromite (chromium (III)), which is normally present in soil as the precipitate $Cr(OH)_3$ (Barnhart, 1997; James et al., 1997). Similarly, selenium can be present as selenates (SeO_4^{2-}) and selenites (SeO_3^{2-}). For vanadium, vanadate (VO_4^{3-}) is the most common form.

Table 7. Metal Cations and Anions

Class	Metals
Metal cations	Aluminum, antimony, barium, beryllium, cadmium, cobalt, copper, iron, lead, manganese, nickel, silver, zinc
Metal anions	Arsenic, chromium, selenium, vanadium

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Metals in their various forms can exist in the pore water as charged species or soluble complexes, or they can precipitate out of solution. Retention of metals by soil is usually electrostatic, with cationic species and anionic species being associated with negatively and positively charged sites on the soil, respectively. For most soils in the United States, negatively charged sites are more plentiful, with less than 5% of the total available charge on the soil surface being positively charged. Therefore, metals existing as cationic species have a greater propensity to associate with the soil. This makes them less bioavailable, but it also results in greater loading of metals into the soil ecosystem. On the other hand, anionic metals generally move into pore water—and so are more bioavailable—but leach out of the system much more rapidly. Soil pH and availability of charged sites on soil surfaces are the primary soil factors controlling release of metals to the pore water and, subsequently, bioavailability.

3.1.7.1. Key Parameters Affecting Metal Bioavailability in Soils

From the preceding overview of how the metals and metal compounds interact with soil constituents, it is clear that soil plays a very significant role in reducing the potential bioavailability of metals in the environment. Given the types of contaminant-soil interactions presented, the primary soil factors controlling the potential bioavailability of metals are identified as soil pH, available charged sites on soil surfaces, clay content, and soil organic matter. The following discussion briefly details the key soil parameters affecting the various contaminants availability to the pore water.

Soil pH: Soil pH is often termed the master soil variable because it controls virtually all aspects of contaminant and biological processes in soil. These processes include solubility, precipitation, speciation, and sorption processes as well as microbial activity. For metals, the net charge of the metal complexes and their precipitation/dissolution reactions are directly impacted by soil pH. Increasing soil pH also results in an increase in the number of negatively charged soil sites, with a concomitant decrease in the positively charged sites. Therefore, increasing the soil pH increases the sorption and removal from the pore water of metal ions (Bohn et al., 1985).

Cation and Anion Exchange Capacities: The available charges on soil surfaces are quantified in the soil parameters known as cation exchange capacity (CEC) and anion exchange

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capacity (AEC). CEC is a measure of the soil's ability to adsorb and release cations, which is directly proportional to the number of available, negatively charged sites. Likewise, AEC is a measure of the soil's ability to adsorb and release anions. As a result, AEC is a measure of available positively charged surface sites.

CEC is directly related to the clay mineral content and type, organic matter, and soil pH. CEC is greater for 2:1 clays such as montmorillonite (600 to 1000 mmol/kg) than for 1:1 clays such as kaolinite (20 to 160 mmol/kg). CEC in organic matter ranges from 2000 to 4000 mmol/kg; however, the organic matter fraction of a soil is usually much less than the clay fraction. CEC arising from pH-dependent charge, which includes organic matter contributions to CEC, increases with increasing pH. CEC in soil ranges from values as low as 10 mmol/kg for extremely coarse-textured soil to as much as 600 mmol/kg for fine-textured soil that contains large amounts of 2:1 clays and organic matter (Bohn et al., 1985).

AEC, which is primarily associated with amorphous oxides, decreases with increasing soil pH. As previously mentioned, the number of positively charged sites (i.e., AEC) on the majority of soil types is very small and, in environmentally relevant pH ranges, is usually negligible. Therefore, AEC is not generally considered an important parameter in assessing contaminant availability at most sites in the United States.

Clay minerals: Clays are soil particles less than 2 microns in size (Miller and Gardiner, 1998); therefore, high-clay soils have higher surface areas relative to sandy soils (sand particle size ranges from 20 microns to 2 mm). Much of the CEC of a soil comes from the negatively charged sites on clay surfaces. Therefore, high-clay soils will have a higher affinity to sorb cationic species due to CEC, thus making contaminants less bioavailable relative to sandy soils. In addition to charged sites available in clays, siloxane oxygens present in clays can interact specifically with contaminants such as the nitro-substituted explosives. Metals can form precipitates with inorganic soil constituents such as carbonate and phosphate minerals under certain soil conditions. Carbonate- and phosphate-metal complexes have varying degrees of solubility and reactivity, depending on the metal, its oxidation state, the ligand to which it is bound, and pH. Precipitation removes a contaminant from the pore water, thus decreasing bioavailability.

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Organic Matter (Organic Carbon) Content: Organic matter includes plant and animal remains in various stages of decomposition, cells and tissues of soil organisms, and substances from plant roots and soil microbes (Sumner, 2000). Organic matter is primarily composed of carbon, oxygen, and nitrogen. Organic matter is often reported or analytically determined on a carbon basis. On average, approximately 58% of organic matter is organic carbon. Soils encompass a range in organic matter, from <1% for a sandy soil to almost 100% for a peat soil, with most soils having organic matter contents <10% (Bohn et al., 1985). Also, organic matter content is usually higher in surface soils or in the root zone and decreases with depth in the soil profile. Organic matter has a high affinity to bind to metals, thereby reducing their availability. The organic acid functional groups typically present in organic matter have a high affinity to attract metal cations.

3.1.7.2. Aging of Metals in Soil

A distinction should be made between persistence of total metals in soil and persistence of bioavailable forms of the metal. As metals "age" in soils, they decrease in bioavailability over time. It has been well documented that metal chemistry in solutions freshly added or spiked into soils vary from metals forms in field-contaminated soils (REF) . Typically, the metal contaminant pool requires time to diffuse into micro- or nanopores and to be absorbed onto organic matter and soil particles. These slow reactions are attributed to micropore diffusion, occlusion in solid phases by (co)precipitation and (co)flocculation, and cavity entrapment. Although the slow reactions play a key role in metal bioavailability, their rates, mechanisms, and controlling factors have not been comprehensively elucidated. Evidence of aging processes is provided by studies of metal extractability and lability (Hamon et al., 1998; Young et al., 2003). It has been frequently observed that easily extractable pools revert with time (~1 year) to more strongly bound forms. Isotopic dilution provides a useful way to quantify changes associated with progressive attenuation of metals in soil. Aging reactions are almost over after about 1 year and are reversible. At present, information regarding the relative importance of aging reactions for different metals and metalloids is very limited, so it is difficult to generalize which metal(s) age the fastest or with greater/less reversibility.

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3.1.7.2.1. Steady-State Calculations for Metals in Soils

3.1.7.2.1.1. *Application*. Aging reactions can be determined empirically by calculating partitioning through measurement of the soil pore water concentration of a metal in well-equilibrated soils. If Kds are calculated from adsorption isotherms, aging must be considered separately. This is related to the high affinity of metals for the soil solid phases, that is, the losses by leaching, erosion, or removal by a crop that is harvested are small when compared with their total concentration. However, for some elements, such as Se, the half-life in soil is significantly shorter. Critical factors that affect the mass balance of metals are the anthropogenic and natural inputs and outputs via leaching to ground water, the removal through surface erosion, and crop harvesting. Excluding erosion processes, the elimination half-life of metals in soil ($t_{1/2}$) can be predicted from a soil mass as:

$$t_{1/2} = \frac{0.69 \times d \times 10000}{y \times TF + \frac{R}{Kd}}$$

where d is the soil depth in m, y is the annual crop yield (t ha^{-1} y^{-1}), TF is the ratio of the metal concentration in plant to that in soil, R is net drainage loss out of the soil depth considered (m^3 ha^{-1} y^{-1}), and Kd is the ratio of the metal concentration in soil to that in soil solution (m^3/m^3).

The time required to achieve 95% of steady state is about four half-lives. This is exemplified in Table 8 for select metals and metalloids. Selenium approaches steady state after only 1 year. As a consequence, Se soil concentrations after 100 years and at steady state are identical. In contrast, concentrations of Cu, Cd, Pb, and Cr III are still well below steady-state values after 100 years and, consequently, their concentrations in soil are very similar. The time necessary to approach steady state is a function of the loading rate and Kd.

3.1.7.2.1.2. *Limitations*. It should be noted that the time needed to approach steady state for all the metals considered, except Se, is in the order of thousands of years, and it is difficult to envisage that soil conditions would not change in this time frame. However, the concept is useful because it provides a time frame within which to consider risk as a function of loading

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capacity of the soils and the potential for continued exposure even after cessation of anthropogenic inputs of metals to soils. Limitations on the application of Kd are discussed in the ground water discussion of this section.

Table 8. Time to achieve 95% of steady-state metal concentration in soil and total soil metal concentrations after 100 years and at steady state[a]

Metal	Loading rate(g ha^{-1} y^{-1})	Kd (L kg^{-1})[b]	T (years)	Soil metal concentration (mg added metal kg^{-1})	
				Steady state	After 100 yrs
Se	100	0.3	1.3	0.01	0.01
Cu	100	480	1860	16	2.4
Cd	100	690	2670	23	2.4
Pb	100	19000	73300	633	2.6
Cr III	100	16700	64400	556	2.6

[a]Assumes a soil depth of 25 cm and a net drainage loss of 3000 m^3 ha^{-1} y^{-1}; background was zero at the start of loading.
[b] Mean Kd (ratio of total metal concentrations in soils to that in pore water) of 49 Dutch soils (De Groot et al., 1998).

Source: Adapted from Smolders et al. (2004)

3.1.7.2.2. Laboratory Methods to Simulate Aging in Soils

3.1.7.2.2.1. *Application***.** The aging effect requires laboratory studies on soils to apply a time-dependent weathering or aging treatment of spiked soils. Critical toxicity values generally are based on toxicological tests performed during the period of relatively fast metal adsorption that follows metal addition to soil. Such values would be smaller than those derived from a similar study conducted with soils a year or more after addition of the metal. McLaughlin et al. (2000) proposed that toxicity thresholds be set using a sequential testing procedure. Tests would be conducted within 2 to 7 days following incorporation of the test substance to generate an estimate of acute hazard. Another set of soils would be tested 60 days after mixing, and a third would be subject to a leaching process and also tested after the 60-day period. The EU has recognized aging as a factor in soil biota toxicity tests. It was estimated that the ranges of reduced toxicity due to aging of metals was a reduction in toxicity of from 1X to 10X. The EU selected a toxicity

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reduction factor of 3X to account for aging in metal toxicity testing (REF). Standardized processes need to be agreed upon for the aging of metals in soil testing.

3.1.7.2.2.2. *Limitations*. The leaching and equilibration times are limited for practical reasons and are meant to simulate some degree of aging and dissolution as a result of weathering. If aging occurs at faster rates than does dissolution, then toxicity will decrease with time. Conversely, if dissolution occurs at a greater rate, then toxicity will increase.

3.1.7.3. Dissolution and Transformation of Metals

3.1.7.3.1. Application

The dissolution and transformation of a metal compound in soil is related to a series of chemical and physical properties characteristic of the compound itself and of the soil. Environmental parameters such as temperature and humidity have a strong influence on the rate of transformation. When assessing the transformation of a compound in soil it should be remembered that aging reactions may take place at the same time as transformation and dissolution. When metal salts are added to soil, the form of the salt dictates the rate and amount of soluble metal that will form in the pore water. Insoluble forms of metals (e.g., vanadium pentoxide [V_2O_5]) will transform to soluble free ion (V) at a slower rate than will soluble metal salts (e.g., Na_3VO_4). However, it must be kept in mind that the rate of formation of the free ion is not proportional to the dissolution rate of the salt, as aging reactions will remove the free ion from the pore water. The relative rates of dissolution and aging need to be considered simultaneously to accurately predict pore water concentrations.

Solution speciation (computer-based models): Computer-based models are based on either equilibrium constants or Gibbs free energy values in order to determine metal speciation from solution chemistry conditions (concentration, pH, Eh, organic complexes, adsorption/desorption sites, and temperature). Both approaches are subject to mass balance and equilibrium conditions that must be controlled. These models have undergone a great deal of development in recent years as reliable thermodynamic data have become available and can provide some predictive estimates of metal behavior. A good review of these models and their

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applications is provided by Lumsdon and Evans (1995). Examples of computer-based speciation models include MINTEQL, REDEQL2, ECOSAT, MINTEQA2, HYDRAQL, PHREEQE, and WATEQ4F.

MINTEQA2 (U.S. EPA, 1991) and VMINTEQ (Gustafson, 2003) both contain subroutines that allow estimates of the importance of metal-organic complexing if the concentration of DOC is known. Perhaps more useful in studies of metals in soil moisture are programs such as WHAM (Tipping, 1994, 1998) and NICA (Gooddy et al., 1995). Application of the chemical speciation model WHAM has been discussed by Tye et al. (2003), who successfully predicted Zn^{2+} and Cd^{2+} activities in soil pore water by assuming the metals were adsorbed by soil humus according to a pH-dependent Freudlich isotherm model. Competitive adsorption between Ca^{2+} and Zn^{2+} and Cd^{2+} could be ignored because it did not improve model fits.

3.1.7.3.2. Limitations

In some instances, metal speciation may be controlled by simple reactions. However, in many cases (particularly in contaminated media), the state of equilibrium and the reversibility of metal reactions are unknown. In addition, these mathematical thermodynamic equilibrium models suffer from other limitations, such as lack of reliable thermodynamic data on relevant species, inadequacies in models to correct for high ionic strength, poorly known reaction kinetics, and complex reactions and lack of models for co-precipitation/adsorption. The first limitation is perhaps the most significant for contaminated media. As an example, none of the models would predict the common, anthropogenic, lead phases of paint, solder, or slag.

3.1.7.4. Soil Metal Transfer to Plants

The “soil-plant barrier” concept was introduced to communicate how metal addition, soil chemistry, and plant chemistry affect risk to animals from metals mixed in soil (Chaney, 1980). Reactions and processes that take place at the soil-plant barrier are influenced by the following factors: (1) solid metal sources (e.g., Fe, Al, and Mn oxyhydroxides and organic matter) may have adsorptive surfaces that influence soil chemistry, (2) adsorption or precipitation of metals in soils or in roots limits uptake-translocation of most elements to shoots, and (3) the phytotoxicity of Zn, Cu, Ni, Mn, As, B, Al, and F, for example, limits residues of these elements

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in plant shoots. More recently, ICP-MS and other very sensitive analytical methods have been used to examine soil solution and soil-plant transfer of 60 elements as a function of soil pH (Tyler and Olsson, 2001a, b). These studies provide evidence that further supports the concept of the soil-plant barrier

For the strongly adsorbed metal cations, the pattern of plant response to metals contained in biosolids has been found to be strongly curvilinear (i.e., plant metal concentration approaches a plateau with increasing soil metal concentration) rather than being a linear plant:soil relationship with increasing concentration. Several areas for potential errors in the research methodology must be avoided when making these comparisons:

- First, comparison of application rates is valid only after the system has equilibrated utilizing accepted methods.

- Second, soil pH levels should be equal across rates studied; co-variance of soil pH should be used to correct for unequal soil pH (Bell et al., 1988).

- Third, the metal concentration in the source applied affects the slope of metal uptake: higher metal concentration in the source means higher phytoavailability at equal metal applications (Jing and Logan, 1992).

3.1.7.4.1. Application/Limitations

It is very clear that strongly acidic soils increase plant uptake of Zn, Cd, Ni, Mn, and Co and increase the potential for phytotoxicity from Cu, Zn, and Ni. In alkaline soils, the high pH increases uptake of Mo and Se. Lead and Cr are not absorbed by plants to any significant extent at any pH (Chaney and Ryan, 1993). However, each element must be considered separately because of its unique chemistry. For example, arsenate is more strongly adsorbed than is arsenite; when a soil is flooded to grow rice, soil microbes can reduce arsenate to arsenite, and the higher concentration of dissolved arsenite can be phytotoxic to rice in more highly contaminated soils. Most other elements have little potential for redox change with change in the redox status of soils. Reduced soils can form sulfide, and sulfide forms low-solubility compounds with most of the metals of concern in soils, including Pb, Zn, Cd, Cu, and Ni (see above discussion on sediment chemistry). For essential elements (e.g., Zn, Cu, Ni), low-solubility species can result in deficiency syndromes. Upon oxidation of the soil, sulfide is

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quickly oxidized, and the metals are returned to more normal equilibrium reactions of aerobic soils.

3.1.8. ATMOSPHERIC CHEMISTRY

Metals are ubiquitous components of particulate matter in ambient air and are emitted by numerous natural and anthropogenic sources. Richardson (2002) included volcanic eruptions and emissions, entrainment of soil and dust, entrainment of sea salt spray, and natural forest fires as significant metals emission sources. Most metals are removed from the atmosphere by deposition and have relatively short atmospheric half-lives. Table 9 presents average atmospheric residence time and airborne concentrations for some metals in California.

Metals have been a major component of EPA air programs. Lead is listed as a criteria pollutant under the CAA, and several other metals are listed as hazardous air pollutants including antimony, arsenic, beryllium, cadmium, chromium, cobalt, manganese, mercury, nickel, and selenium. Approximately one-third of these have concerns related to speciation. Deposition of metals from the atmosphere is under consideration by the Office of Water (U.S. EPA, 2003). This latter program is primarily concerned with deposition, speciation, and transformation after deposition of mercury, although lead and cadmium are involved to a lesser extent. The State of California has a comprehensive program for monitoring airborne metals through its Air Toxics Monitoring Network.

For over half of the metals, EPA does not consider bioavailability or speciation in risk assessment of atmospheric metals; rather, risks are assessed on the basis of total or respirable airborne metal concentrations (U.S. EPA, 1998). EPA assesses risks for lead with a set of pharmacokinetic models known as the integrated exposure uptake biokinetic (IEUBK) and adult lead models (see Section 3.2 Exposure). Although these models explicitly consider oral bioavailability of lead, they do not consider inhalation bioavailability.

Metal speciation and chemistry have not been significant components of EPA's evaluation and assessment of environmental metals. The impetus toward a more comprehensive evaluation of metals must start with qualitative and quantitative toxicology. If there is a

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significant difference among the various atmospheric metal species with respect to toxicology (as is the case with divalent and elemental mercury), then expenditure of resources on environmental fate models, development of analytical techniques, and monitoring may be warranted. To some extent, the mercury Report to Congress (RTC) (U.S. EPA, 1997) is a paradigm for a complete multimedia exposure and risk assessment for metal species and may be used as a benchmark by EPA for the development of similar efforts for other metals.

3.1.8.1. Applications/Limitations

A substantial part of the atmospheric chemistry of metals takes place in the aqueous phase, where it is not significantly different from aqueous chemistry in other media. Constructs (e.g., pH/Eh diagrams and geochemical computer models) may be used to determine metal speciation in atmospheric aquatic aerosols. However, the application of such diagrams and models, which assume that metal species are in chemical equilibrium, must be limited to describing metal speciation reactions that can equilibrate in seconds or less. These include many acid/base and metal complex formation reactions but not most reactions involving adsorption, oxidation/ reduction, or mineral precipitation. Atmospheric metal reactions that take longer to equilibrate must be studied in terms of their reaction kinetics rather than equilibrium chemistry.

Table 9. Atmospheric Metals

Metal	Residence Time	Average Concentration (ng/m^3)
Arsenic	Unknown	2.4 ng/m^3
Cadmium	7 days	1–2.5 ng/m^3
Nickel	Unknown	7.3 ng/m^3
Beryllium	10 days	0.11–0.22 ng/m^3
Lead	7–30 days	270–820 ng/m^3
Mercury	.3–2 years	0.37–0.49 ppb

Source: Adapted from Seinfeld and Pandis (1998)

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Seinfeld and Pandis (1998) present a detailed discussion of the acid-base chemistry of atmospheric water that may be useful in modeling metal speciation. In addition, sorption to particles, deposition, and gas-phase redox chemistry may be important for some metals (Bodek et al., 1988). Deposition is largely a function of the properties of particles, not the sorbed or incorporated metals. Redox chemistry takes place through oxidation with free radicals such as OH or through direct photolysis of metal complexes (Finlayson-Pitts and Pitts, 1986). Due to the oxidizing nature of the atmosphere, metals are often converted to their most oxidized stable forms.

Most sampling and analytical techniques published by EPA for metals in air are oriented toward evaluation of particulate-phase total metals rather than metal species (U.S. EPA, 1999a). These methods involve collection of either total or respirable particulate fractions, with subsequent analysis by X-ray fluorescence, atomic absorption, inductively coupled plasma, proton-induced x-ray emission, or neutron activation analysis gamma spectroscopy techniques. The one notable exception is a method for mercury (Method IO-5) that speciates vapor and particulate forms. To the extent that metals are sorbed to particulate phases, analysis of individual metal species can, at least theoretically, be accomplished by the same techniques used to analyze those species in other solid media.

Of all the metals of interest, mercury has the most complex and best understood atmospheric chemistry (Lindqvist, 1994; Munthe, 1994). In the gas phase, mercury is oxidized by O_3 and NO_2; aqueous-phase chemistry includes oxidation of elemental mercury by free radicals such as OH and HO_2. Both vapor-phase and aqueous atmospheric chemistry may involve heterogeneous-phase components. EPA has made a substantial effort to evaluate the atmospheric fate of mercury due to the requirements of the CAA. U.S. EPA (1997) contains a complete qualitative and quantitative evaluation of mercury's atmospheric fate based on the state of knowledge when the report was written. EPA is also working with the University of Wisconsin to quantify mercury transformations in the atmosphere, including depositional behavior.[5]

[5]EPA Grant R829798. Project officer: Bill Stelz, NCER.

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3.1.9. METALS SPECIATION TECHNIQUES

A wide variety of analytical and chemical techniques have been used to characterize metal speciation in various media (Hunt et al., 1992; Manceau et al., 1996, 2000; Welter et al., 1999; Szulczewski et al., 1997; Isaure et. al., 2002; Lumsdon and Evans, 1995; Gupta and Chen, 1975; Ma and Uren, 1995; Charlatchka et al., 1997). These techniques provide information on speciation, particle size, and the source of the metal and also quantitatively determine the metal level present. Of the techniques tested (physicochemical, extractive, and theoretical), the tools that have been used most often to evaluate speciation include the following.

Particle-bound metal: For particle-bound metal, tools include x-ray absorption spectroscopy (XAS), x-ray diffraction (XRD), particle-induced x-ray emission (PIXE and μPIXE), electron probe microanalysis-scanning electron microscope (EPMA-SEM), secondary ion mass spectrometry (SIMS), and x-ray photoelectron spectroscopy (XPS)—sequential extractions, single chemical extractions.

Over the past decade, numerous advances in materials science have led to the development of a wide range of analytical tools for determining metal concentrations, bonds, and valences of individual particles on a scale that can be considered useful for the speciation of environmentally important materials (soils, wastes, sediments, and dust). Although most of these tools are scientifically sound and offer important information on the mechanistic understanding of metal occurrence and behavior, only a few provide currently useful information on metal bioavailability for use at a “site” level (see Table 10). However, other techniques may still be essential for conducting a detailed characterization of a selected material to describe the chemical or kinetic factors controlling the release, transport, and/or exposure of a metal.

An indirect approach to speciation, in contrast to the direct methods previously described, includes functional or operational extraction techniques that have been used extensively (Tessier and Campbell, 1979, 1988; Gupta and Chen, 1975). These methods use either a single or a sequential extraction procedure to release species associated with a particular metal within a medium.

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Single-chemical extractions: These methods generally are used to determine the bioavailable amount of metal in a functional class (e.g., water soluble, exchangeable, organically bonded, Fe-Mn bound, or insoluble). In a similar approach, sequential extractions treat a sample with a succession of reagents that are intended to specifically dissolve different and less available phases. Many of these techniques are a variation on the classical method of Tessier et al. (1979) in which metal associated with exchangeable, carbonate-bound, Fe-Mn bound, organically bound, and residual species are determined. A number of excellent reviews on the use and abuse of extraction techniques are available (Beckett, 1989; Kheboian and Bauer, 1987; Foerstner, 1987). These techniques can be useful in a study of metal uptake by plants and soil invertebrates, where transfer takes place predominantly from a water solution phase. However, these methods are not "selective" for metal species, and these leachable fractions have never actually been correlated to bioavailability.

Plants: When considering the bioavailability of a metal to plants from soil and sediments, it is generally assumed that both the kinetic rate of supply and the speciation of the metal to either the root or the shoot are the most important factors. In soils and sediments, there is generally a small volume of water in contact with the chemical form of the metal. Although the proportion of soluble metal in pore water is small when compared with the bulk soil/sediment metal concentrations, it is this phase in pore water that is directly available to plants at the root tips. Therefore, understanding pore water chemistry is critical; that is, measuring metal concentrations as simple inorganic species, organic complexes, or colloid complexes is most important. Tools currently used for metal speciation in plants include:

- In situ measurements using ion selective electrodes (Gundersen et al., 1992; Archer et al., 1989; Wehrli et al., 1994).
- In situ collection techniques using diffusive equilibrium thin films and diffusive gradient thin films followed by laboratory analyses (Davison et al., 1991, 1994; Davidson and Zhang, 1994; Zhang et al., 1995).
- Equilibrium models (SOILCHEM) (Sposito and Coves, 1988).

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Table 10. Characteristics for Direct Speciation Techniques

Tools	Species lability	Species particle size	Species valance state	Species bonding	Species composition	Species abundance	Element specificity	Isotopic character	Element sensativity	Resolution	Availability	Cost
XRD	No	No	No	No	No[a]	No	No	No	3–4 vol%	Bulk	1	$
EMPA/SEM	Yes	Yes	Yes[b]	No	Yes	Yes[e]	B-U	No[d]	100 ppm	.5-1 μ	2	$$
SIMS	No	Yes	No	No	Yes[e]	Yes[f]	Li-U	Yes	1 ppb	10 μ	4	$$$
XPS	No	No	Yes	Yes	Yes[e]	Yes[f]	H-U	No	wt.%	100 μ	2	$$
XAS	No	No	Yes	Yes	Yes[e]	Yes[f]	He-U	No	ppb	2 μ	5	$$$$
PIXIE	No	No	No	No	Yes	Yes[f]	B-U	No	10 ppm	4 μ	4	$$$$

[a] Identifies crystalline compounds and stoichiometric compositions only.
[b] Valence determined by charge balance of complete analyses.
[c] Technique has limitations based on particle counting statistics.
[d] Limited when combined with ICP/MS/LA.
[e] Technique requires each element be tuned and standardized, requiring unreasonable time limits.
[f] Techniques designed and tested only on simple systems. Multiple species require lengthy analytical and reduction.

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3.2. EXPOSURE PATHWAY ANALYSIS

Risk is a function of both hazard (i.e., the intrinsic toxicity of a substance) and level of exposure. The route of exposure, as well as other details such as timing and duration, is also important because exposures vary in their effectiveness in delivering a dose across a biological boundary (Ott, 1985; Ryan, 1998). No risk exists unless an effective exposure to a receptor occurs.

> Metal exposure assessment includes consideration of the exposure routes and pathways specific to metals, phase associations and chemical forms of the metals, and the expression of exposure and target doses in a manner consistent with defining hazard thresholds for particular organisms.

Exposure routes include inhalation, ingestion, and dermal or, for plants, root uptake and leaf exposures. **Pathways** describe the specifics of any exposure and include transport of the contaminant in the environment as well as exposure route for individuals of concern (e.g., inhalation of lead in dust by children playing in a park near a busy highway or dietary ingestion of a soil contaminant that has been taken up by plants). **Phase association** and **chemical speciation** influence metal movement through pathways and the metal's capacity to deliver a dose to receptors of concern.

Major metal sources to waters and lands include diverse manufacturing, mining, combustion, and pesticide activities. Major atmospheric sources are oil and coal combustion, mining and smelting, steel and iron manufacturing, waste incineration, phosphate fertilizers, cement production, and wood combustion (Haygarth and Jones, 1992). Metals from these atmospheric sources can find their way into soils, sediments, and water. Other major sources to aquatic and terrestrial systems include chlor-alkali, acid, pigment, electronics, and copper sulfate production.

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Some exposure assessments do not involve anthropogenic releases of metals to the environment. Rather, they focus on changes in exposure to ambient metals that result from other aspects of human activities. For example, acidification of freshwater changes aluminum phase association and speciation, resulting in an increased dose of naturally occurring metals to aquatic biota (e.g., Campbell et al., 1992). Intensive irrigation mobilizes selenium that is naturally present in relatively high concentrations in western soils, and consequent evaporative concentration in wetlands, impoundments, and other low-lying areas in arid regions of the U.S. can lead to toxic exposures (e.g., Wu et al., 1995).

> When the molar concentration of acid-volatile sulfide (AVS) in sediment exceeds the amount of simultaneously extracted metal (SEM) (SEM-AVS < 0), then the metals are expected to associate with the solid phase rather than interstitial water.

This section first describes methods for assessing transport of metals through various media (water, soil, air). Exposure routes for humans are then discussed, with attention paid to how to quantify target dose (i.e., account for bioavailability differences). A discussion then follows of exposure to aquatic organisms through water and dietary routes, looking again at models to account for site-specific differences in bioavailability. The section concludes with similar discussions about quantifying exposure to metals for terrestrial organisms.

3.2.1. AQUATIC AND TERRESTRIAL TRANSPORT PATHWAYS FOR METALS

Metals move through the environment in dissolved forms where they follow water pathways, as part of particles in air or soils, or as gases. During exposure assessment, models of metal transport (e.g., state partitioning models) and fate (e.g., aging reactions) are used to predict concentrations in the various environmental compartments. Most models have been developed for steady-state equilibrium conditions due to the relative ease of parameterization, but in recent years a greater effort has been directed toward predicting fluxes prior to steady state as well as conditions following pulse exposures. Many of the models used for metals predictions were

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originally developed and used for organic substances, whereas others are specific to metals. This section provides an overview of such models, with particular attention to application for metals assessment. Detailed discussions are found in Paquin et al. (2003) for aquatic systems and Allen (200?) for terrestrial systems.

3.2.1.1. Aquatic Transport

Modeling of metal transport and fate within aquatic systems includes hydrodynamic or fluid transport models to simulate movement of water and dissolved metals, particle transport models for sorbed metals (primarily as sediment transport), and transfer kinetics to simulate exchange between the water column and sediments (Figure 6). The output of the modeling exercise is an estimate, over time and space, of the concentrations of the metal(s) of concern in the water column and sediments.

Modeling movement of metals through the aquatic system begins with a characterization of movement of water through the system. The system's hydrodynamics define the time scale of the remainder of the analysis because they define the residence time of the metals within the various parts of the system. Fluid transport also is responsible for dilution and mixing chemicals within receiving waters. Sediment transport is also influenced by water movement, including settling and resuspension, scouring, and local movements. The analysis of chemical reactions and fluxes, such as biodegradation, photooxidation, and volatilization, also are included in fate analysis. These can lead to chemical equilibrium models that predict the amount of free ion available for complexation with biotic ligands and, ultimately, the toxic fraction of total metals.

Several reviews of fate and transport models, without particular emphasis on metals, have been completed since the early 1980s. The most recent was by Paquin et al. (2003), who reviewed exposure, bioaccumulation, and toxicity models for aquatic systems. EPA has published a review describing the use of modeling tools for the development of total maximum daily loads (TMDLs) in watersheds (U.S. EPA, 1997). An earlier review by the Agency (U.S. EPA, 1987) looked at all surface water quality models for use in exposure assessments. Schnoor et al. (1987) published their review at the same time and included detailed descriptions of fate and transport models and their required input parameters.

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Earlier publications include those provided by Delos et al. (1984), who reviewed models for wastewater load allocations, and Mills et al. (1985), who described screening-level analyses for water quality assessments of conventional pollutants. However, because of the advances during the past 10 years (from approximately 1995) in developing fate and transport models specifically for metals (including recent efforts to couple these models with metal speciation models and more sophisticated stand-alone hydrodynamic and sediment transport models), only the reviews by Paquin et al. (2003) and U.S. EPA (1997) provide information relevant to metals assessments.

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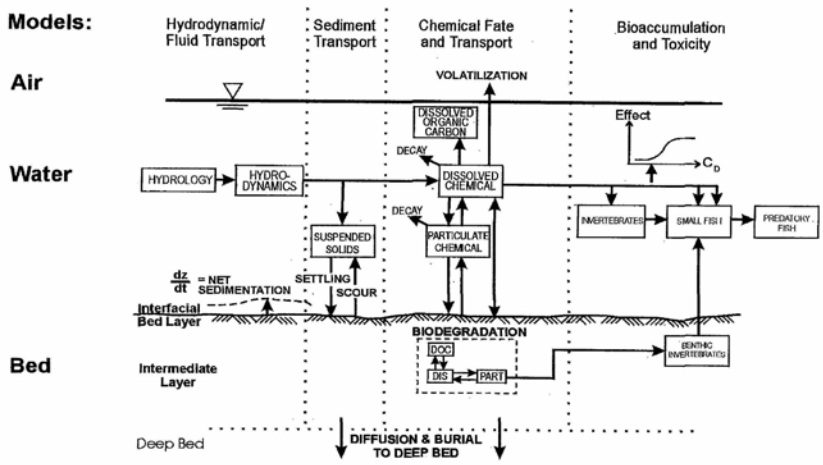

Figure 2-2 Example modeling framework

Figure 6. Modeling framework for fate and transport of metals in aquatic systems

Source: Paquin et al., 2003

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3.2.1.1.1. Applications

Predictions of fate and transport of metals in aquatic systems is best accomplished through the use of integrated models rather than sophisticated stand-alone hydrodynamic or sediment transport models. Although these more sophisticated models are useful for examining and developing input parameters for the integrated models, they do not handshake well with each other, thus introducing large uncertainties when assessing the system as a whole. The exceptions are chemical speciation models that are vital both for input to fate and transport models and for predictions of bioavailability.

> The fate and transport of metals in aquatic systems is most reliably predicted using integrated models, rather than stand-alone hydrodynamic or sediment transport models.

A list of aquatic system fate and transport models is provided in Table 11, and also discussed in the bullets below. These models were selected because of their widespread acceptance and use by the regulatory community and because they include features of particular usefulness for metals (Paquin et al., 2003). Analytical solution models are the simplest models with the lowest computational requirements. They are solved analytically to provide concentrations of metal of time or space.

> Analytical solution models of aquatic system fate and transport are the simplest models with the lowest computational requirements. They are solved analytically to provide concentrations of metal of time or space.

- Water Quality Assessment Methodology (WQAM) model: In addition to being a modeling tool, it is a collection of methods and data tables that describe simple screening-level procedures to water quality assessments. It provides a useful general review and approach, although there are few metal-specific attributes.
- River Risk (RIVRISK) model: This is the only model in the list that includes a bioaccumulation subroutine. However, it is a proprietary model of the Electric Power Research Institute and is available only to registered users.

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- Simplified Lake and Stream Analysis (SLSA) and General Motors III models: These are modifications of the Simplified Lake and Stream Analysis (SLSA) program (DiToro et al., 1981; HydroQual, 1982; DiToro, 1987) and describe a one-dimensional stream and completely mixed lake. They have incorporated more sophisticated routines to describe variable geometry of stream channels and are also applicable to multiple, constant geometry river reaches.
- Donald J. O'Conner (DJOC) model: Represents a series of papers providing additional algorithms for inclusion in the SLSA model.
- Quantitative Water Air Sediment Interaction (QWASI): A fugacity model applicable to lakes and rivers to simulate the exchanges of chemicals with measured vapor pressure between air, water, and sediments (the Unit World Model for organic substances). The model has been coupled with MINEQL to allow for interconversion of species and consideration of metals in dissolved, colloidal, and particle phases in water. It is known as the TRANSport and SPECiation (TRANSPEC) model (Bhavsar et al., 2004) and is not yet applicable to sediments.
- Uniform System for Evaluation of Substances (USES) model: This tool was developed in Europe to model dissolution and movement of antifoulant paints on boats. It is a simplified approach to estimating metal concentrations in a completely mixed water body, and it has largely been replaced by the much more complex version, the European Union System for the Evaluation of Substances (EUSES) (Berding et al., 1999). Software for this model is available (EC, 1996a), and the model has been successfully applied to metals.

> Numerical modeling of aquatic systems fate and transport can represent more complex geometry and transport regimes than can be simulated using analytical solution models.

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The remainder of the models listed in Table 11 and described in the following bullets are numerical solution models. The first four assume steady-state conditions, and the remainder are time-variable models. Numerical models can represent more complex geometry and transport regimes than can be simulated using analytical solution models.

- Chemical Transport and Analysis Program (CTAP): This program model is essentially the numerical solution version of the SLSA model and extends the model to two- and three-dimension systems as well as to multiple particle sizes and types.
- Pawtuxent Toxics (PAWTOXIC): This is a relatively simple one-dimensional model for estimating particle deposition and resuspension in river and streams, assuming equilibrium partitioning (EqP) conditions. It does not, however, include exchange of dissolved metals between water and sediments.
- Simplfied Method-Program Variable-Complexity Stream Toxics (SMPTOX): This model is another in the family of models derived from SLSA, and it is also a one-dimensional representation of rivers and streams. It is, however, a Windows-based model, which makes it simpler for inexperienced users. Unlike PAWTOXIC, it does include diffusive flux modeling of movement of dissolved metals between water column and sediments. Additionally, it incorporates AVS-SEM (see Section 3.4) for copper, cadmium, nickel, lead, and zinc, but it does not consider oxidation of other metals.
- Metals Exposure Analysis Modeling Systems (MEXAMS): Links EXAMS (a widely used fate and transport model developed by EPA) with MINTEQ, a chemical equilibrium model (Felmy et al., 1984; see Section 3.1. Environmental Chemistry for further discussion of MINTEQ). MEXAMS has not yet been coupled with EXAMSII (a time-variable model), so it can only handle steady-state systems. EXAMS can be applied to a one-, two-, or three-dimensional system and includes an interactive bed layer. By transferring total metal concentrations to MINTEQ in an iterative process, EXAMS is able to calculate fate and transport of

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metal species, although it is limited to bulk exchange of particles between water and sediment.

The last 11 models listed in Table 11 are time-variable models that also can be used to simulate steady-state conditions, such as determining simple waste load allocations during critical low flow conditions. However, due to the complexity of setting up and parameterizing these models, it is recommended that they be used only for more complex situation in higher-tiered analyses.

The steady-state models described above are sufficient for the situations where simplification is acceptable. One exception is the most recent version of EXAMS (EXAMSII, Version 2.97), which can be run in both steady-state and time-variable modes. The following provides additional information on the numerical time-variable models listed in Table 11.

> While the time-variable models listed in Table 11 can be used to simulate steady-state conditions, it is recommended that they be used only for more complex situations in high-tiered analyses due to the complexity of setting up and parameterizing them. Generally, steady-state models are sufficient when simplification is acceptable.

- Exposure Analysis Modeling System II (EXAMSII, Version 2.97): The greatest limitation of this model is its representation of water column-bed interactions by a bulk exchange of water and particles. However, it is has been widely used for many years and therefore has the advantage of being able to quickly move between simplified steady-state assumptions and more realistic (albeit more complex) time-variable analyses.
- River Quality II (RIVEQLII): This model was developed specifically for inorganic substances. It incorporates sophisticated chemical equilibrium calculations through linking with MINEQL (Westall et al., 1976; see Section 3.x.x. Environmental Chemistry Speciation for further discussion of MINEQL).

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RIVEQLII is applicable to one-dimensional rivers and streams. It assumes equilibrium conditions and incorporates particle setting to the bed, sorption reactions, and precipitation and dissolution of chemical to and from the sediment bed.

The WASTOX, RCATOX, and WASP5 models listed in Table 11 and described below evolved out of an earlier model, the Water Quality Analysis Simulation Program (WASP), plus parts of SLSA and CTAP (DiToro et al., 1981).

- Water Quality Analysis Simulation of Toxics (WASTOX) model: This model was the first to build on the WASP and others and mostly incorporates their subroutines.
- Row-Column AESOP for Toxics (RCATOX) model: This model reflects the evolution of WASTOX, and uses parallel processing supercomputers for greater speed. It is still undergoing testing and has not yet been released for general use.
- Water Quality Analysis Simulation Program, Ver. 5 (WASP5): This is the current version of the early WASP model and is currently supported by EPA. Essentially, WASP5 incorporates EXAMS with refined sediment transport capabilities. WASP5 is distributed with two different subroutines: EUTRO, which is used in eutrophication problems, and TOXI5 for simulating fate and transport. The WASP5 package also includes an associated food chain model. Most importantly, WASP5 and RCATOX are designed to interface with state-of-the-art hydrodynamic and/or sediment transport models, a feature not shared by any of the other available fate-and-transport models. This has application to estuarine and coastal systems with complex hydrodynamic conditions. WASP5 interfaces with the PC-compatible hydrodynamic model DYNYD5 (Ambrose et al., 1993). WASP5 and RCATOX can both interface with the Estuary, Coastal, Ocean Model (ECOM), a family of hydrodynamic models (Blumberg and Mellor, 1987), and with ECOMSED (HyroQual, 1998), a sediment transport model.

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- Delft 3D Model (DELFT3D): The DELFT3D model was developed by Delft Hydraulics Lab in The Netherlands and is a flexible integrated model that includes the following modules: hydrodynamics, water quality (including sediment transport), chemistry, and wave generation. The model is proprietary software but is available commercially. The Hydrologic Simulation Program-FORTRAN (SPF) model is the most recent version of a family of models originally developed in the 1960s. It is unique in that it includes hydrology and nonpoint-source terrestrial runoff modules, for which it is primarily used. It is applicable to complex watersheds and provides information for continuous input simulations or for storm events. It models well-mixed reservoirs as well as branched river systems and can include up to three sediment types. It has been widely used throughout the US, but its sophistication limits its use to experienced modelers.

Sophisticated representations of sediment transport mechanisms are included in the Channel Transport (CHNTRN) model, the Sediment/Radionuclide Transport Model (FETRA), and the Sediment Contaminant Transport model (SERATRA).

- CHNTRN model: This is a one-dimensional, time-variable model that simulates chemical fate in well-mixed estuaries and includes sand, silt, and clay using degradation and sorption processes from EXAMS.
- FETRA model: This is a two-dimensional, depth-averaged model for estuaries and coastal areas that includes decay, settling, and resuspension of solids as well as sediment transport.
- SERATRA model: This is also a two-dimensional model with features similar to FETRA, but it is applicable to rivers.

The final model listed in Table 11 is RECOVERY, a model supported by the U.S. Army Corps of Engineers. The model represents a well-mixed surface-water layer underlain by a

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vertically stratified but horizontally well-mixed water column. The sediment is defined by three zones (surface, deep contaminated, and deep clean), which can be further subdivided on the basis of porosities, contaminant concentrations, and other factors. RECOVERY is used for evaluating sediment capping scenarios and sites with old contamination (where clean sediment has layered over the contaminated bed). Additional models that are not listed in Table 11 include:

- Site-specific models such as the copper fate and transport model for San Francisco Bay (Chen, 1996) and MIKE21, a three-dimensional numeric model for fate and transport plus a hydrodynamic model for rivers developed by the Danish Hydraulic Institute.
- Metal Exposure and Transformation Assessment Model (META4) model, which is the WASP5 transport model combined with the MINEQL speciation model. It is used for developing TMDL waste load allocations, and evaluating remedial actions and TMDLs (Martin and Medine, 1998). It is applicable to a variety of receiving waters, including ponds, streams, rivers, lakes, and estuaries, and can be run as one-, two-, or three-dimensional systems. The META4 model addresses some of the shortcomings in WASP4 to more accurately describe metal dynamics by, for example, the recent addition of subroutines to represent the interactions of dissolved metals with iron oxyhydroxides in the water column and sediment under variable pH and the ability of the model to predict future concentrations of the major cationic metals under variable regimes of water chemistry. It also handles numerous point and nonpoint loads and sequential deposition or scouring of sediment bed layers.

Water quality analyses often require probabilistic results, as the water quality criteria (WQC) specify not-to-exceed concentrations for a once-in-a-3-year return period. Steady-state models cannot evaluate a return period for exceedences. When using these models, a Monte Carlo analysis can be conducted to generate a large number of model inputs and subsequent solutions that can then be analyzed statistically to characterize the exceedence probability. Time-

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variable models that generate long-term simulations (e.g., 20 years) can also be statistically analyzed to evaluate the frequency of exceedences. Several statistical models have been developed specifically for conducting these types of analyses. The Probabilistic Dilution Model (PDM) (Di Toro, 1984) is one such model. Program Monte (HydroQual, 1997) is a Monte Carlo program that generates a time series of daily concentrations. The Dynamic Toxics (DYNTOX) model (LTI, 1994) is an EPA model that uses three statistical methods to predict the frequency of water quality standard violations. RIVRISK, one of the steady-state analytical solution models described above, contains a built-in Monte Carlo simulator.

Further detailed discussions about uses and limitations of all the models discussed above are provided by Paquin et al. (2003). Additional models required for specialized regions of water bodies, such as mixing zones or plumes, are also listed in Paquin et al. The appendix contains the source for obtaining all the models discussed

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Table 11. Fate and Transport Models

Abbreviation	Model name
Analytical solution models	
WQAM	Water Quality Assessment Methodology
RIVRISK	River Risk
SLSA	Simplified Lake and Stream Analysis
GMIII	General Motors III
MICHRIV	Michigan River
DJOC	Donald J. O'Conner (1988), a triad of papers
QWASI	Quantitative Water Air Sediment Interaction
USES	Uniform System for Evaluation of Substances (replaced by EUSES; 1996)
Steady-state numerical solution models	
CTAP	Chemical Transport and Analysis Program
PAWTOXIC	Pawtuxent Toxics
SMPTOX3	Simplified Method Program-Variable-Complexity Stream Toxics
MEXAMS	Metals Exposure Analysis Modeling System (includes EXAMS and MINTEQ)
Time-variable numerical solution models	
EXAMSII	Exposure Analysis Modeling System II
RIVRQLII	River Quality II
WASTOS	Water Quality Analysis Simulation of Toxics
RCATOX (AESOP)	Row Column AESOP for Toxics (AESOP: Advanced Ecological Systems Operating Program)
WASP5	Water Quality Analysis Simulation Program, Version 5; distributed with DYNHYD5, Dynamic Hydrodynamics 5
DELFT3D	Delft 3D Model
HSPF	Hydrologic Simulation Program - FORTRAN
CHNTRN	Channel Transport Model
FETRA	Sediment/Radionuclide Transport Model
SERATRA	Sediment Contaminant (i.e., radionuclide) Transport
RECOVERY	RECOVERY

Source: Paquin et al. (2003)

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3.2.1.1.2. Limitations

Most models of transport and fate of metals in aquatic systems assume EqP of metals between water (dissolved) and particles (sorbed). Further, the magnitude of the partition coefficient is described in proportion to the amount of dissolved organic matter (DOM) (generally quantified by the amount of dissolved organic carbon (DOC)). This is the single most important parameter in modeling metal movements because the sorbed metal is transferred between water and sediment compartments in proportion to the amount of settling and reexchange of particles, and flux of metals into sediment porewater is proportional to total dissolved metal (free ionic forms + amount complexed with DOC). Partitioning reactions also determine the amount of bioavailable metal. However, assuming equilibrium conditions is a known oversimplification of most systems and results in considerable uncertainty in estimates of dynamic systems or situations where metals are either continuously being discharged or immediately following a pulse exposure.

An important parameter in modeling the fate and transport of metals in aquatic systems entails describing the magnitude of the partition coefficient in proportion to the amount of DOM, quantified by the amount of DOC, because 1) sorbed metals are transferred between water and sediment compartments in proportion to the amount of settling and reexchange of particles, and 2) flux of metals into sediment porewater is proportional to total dissolved metal (free ionic forms + amount complexed with DOC).

Many models that were initially developed for organic substances assume first-order decay processes. These are of little importance for metals, but they sometimes are used in screening-level assessments to represent removal of sorbed material from the water column. They are overly simplistic and should be used with caution. Given the capacity of most computing environments today, it is likely that metal-specific sorption and water-sediment flux models can be used even for simple assessments.

Modeling of mercury and metalloids such as arsenic and selenium is complicated by transformation processes that change the form of the metal. Methylation of mercury and arsenic or binding of selenium to amino acids (e.g, selenomethioine) changes both their physical and

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biological properties (see Section 3.1.3. for a discussion of transformation processes). Similarly, metals that readily change oxidation state (e.g., chromium) also require additional considerations in fate modeling. Many of the same transport models can be used, but input parameters will require modification. Such models are beyond the scope of this Framework, whose focus is on inorganic forms of metals. See, for example, the Mercury Cycling Model by Hudson et al. (1994) for further guidance on fate and transport models for mercury.

All modeling exercises are limited by the validity of the model framework, the accuracy of input parameters, and the experience of the analyst (Dzombak and Ali, 1993). All exposure assessments should include an explicit description of model assumptions and associated uncertainties.

3.2.1.2. Terrestrial

Movement of metals through soils is dependent on chemical properties controlling speciation, the presence of ligands that control complexation of metals within pore water (and groundwater) and adsorption onto mineral surfaces, and rate of water flux through the soil. Metals are lost from the soil primarily by leaching into groundwater, although in some particular instances uptake by plants can represent a significant loss. Section 3.1.5. reviews the processes and models that predict movement of chemicals through soils or partitioning onto mineral surfaces (i.e., partition coefficients). These serve the same role as the fate and transport models discussed above for aquatic systems and therefore are not repeated here.

3.2.2. Routes of Exposure to Humans

Assessment of human exposures to any chemical agent includes (1) identifying pathways by which chemicals in the environment can make contact with humans, (2) determining the concentrations of the chemical agent in all relevant physical and chemical forms and in the primary media of human contact, (3) estimating intake rates and amounts in

> ***Ingestion*** is the primary route of exposure for humans, with inhalation and transplacental transmission being important secondary. When air serves as the primary medium of contact, inhalation is the major pathway for human intake of metals.

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those media through all relevant physiological routes of entry to the body, (4) describing and, where possible, quantifying relationships between exposure concentrations and intakes, and (5) identifying sources of uncertainty and natural variability and, where possible, quantifying these in estimates of exposure.

Routes of entry of metals into humans that are most frequently encountered in metals risk assessments are ingestion, inhalation, and transplacental transmission; dermal absorption is not a primary exposure route for metals. The pathways discussed here include air, surface dust and soil, food, water, and transplacental transmission. Although dermal contact with metals in soil, through atmospheric deposition, or from water during swimming or showering represents a potential route of exposure, the relatively low lipid solubility of most metals limits absorption through the skin (Hostynek et al. 1998; Paustenbach, 2000), with the exception of Hg^0. Therefore, this route of exposure is not considered in the discussions below. Furthermore, in most instances in which airborne metals have resulted in environmental contamination, ingestion of surface dust tends to be the dominant contributor to human health risk.

3.2.2.1. Air Pathway and Inhalation Exposure

Inhalation is the major pathway for human intake of metals in which air serves as the primary medium of contact. Other indirect pathways in which air serves as an antecedent medium include:

- Deposition of metals to surface dusts and subsequent intake from ingestion or inhalation;
- deposition to surface water and sediment and intake from ingestion; and
- uptake of deposited metals into or onto aquatic and/or terrestrial biota, entrance into the human food chain, and intake from ingestion.

The bioavailability of inhaled metals can be much higher than that of other routes of intake. This may result in relatively high internal doses even when intakes are similar to those from other routes. An example is the large contribution made by cigarette smoking to the body burden of cadmium (e.g. Ellis et al., 1979; Friis et al., 1998). Infants and children can be particularly vulnerable to airborne metal particles, because variations in airway structure and respiratory conditions (e.g., as with age) may alter the deposition pattern of inhaled particles,

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which may contribute to variations in bioavailability (James, 1994; Phalen et al., 1985; Xu and Yu, 1986).

3.2.2.1.1. Application

Human exposures to airborne metals or other contaminants are usually associated with metal-bearing particles in the PM10 fraction (i.e., particles that are less than or equal to 10 microns in diameter). Larger particles do not penetrate far into the respiratory tract. This necessitates measuring particle sizes in the breathing zone of potentially exposed people to achieve accurate estimates of deposition amounts and rates in the respiratory tract. This may be accomplished through the use of stationary samplers, although personal dosimeters are used in particular site assessments. Additional information required to estimate inhaled dose is the same as for any other chemical and includes inhalation rate, tidal volume of the lungs (age and sex specific), and body size. U.S. EPA (1997) contains the required information. However, reference concentrations (RfCs) used in most assessments of human health risks from inhalation only require measurement of total concentration of the metal of concern in air. The RfC is based on dosimetry methodology (U.S. EPA 1994) and already incorporates exposure variables of inhalation rate, etc.

3.2.2.1.2. Limitations

The use of stationary air samplers to estimate human exposure may involve key assumptions that introduce uncertainties into exposure estimates. Air concentrations measured at stationary samplers will not incorporate exposures from multiple locations (e.g., from inhalation of dust by riders of off-road vehicles moving across a contaminated site) (Azar et al., 1975). Simply measuring total metals introduces uncertainties into inhalation exposure estimates, because the metal species affects mechanisms, rate, and extent of absorption from the respiratory tract (Oberdoerster, 1992; Bailey and Roy, 1994). Lack of information about particle sizes, chemical form, and solubility of airborne metals in the breathing zone has important implications for accurate modeling of rates of absorption and subsequent internal dose (Khoury and Diamond, 2003). In addition, for a few metals airborne particles may result in toxic effects due to dermal

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penetration (e.g., Cr may cause dermal toxicity and Hg may be absorbed with resultant effects on the nervous systems).

3.2.2.2. Surface Dust and Soil Pathway

Surface dusts and soil are particularly important media of human contact with metals because both serve as repositories for airborne metal particles. As a result, exposures can occur long after cessation of emissions of metals to air. Humans are exposed to metals in surface dust and soil primary through incidental ingestion or from inhalation of suspended dust particles. Dermal contact with metals in soil represents another potential route of exposure, but the relatively low lipid solubility of most metals generally limits absorption through the skin (Hostynek et al., 1998; Paustenbach, 2000). However, few studies have actually attempted to quantify the extent or kinetics of dermal penetration of metals deposited on the skin, and the applicability to these studies to metal species and complexes that occur in surface dust or soil is highly uncertain.

> **Infants and children** are particularly vulnerable to incidental exposures to metals in surface dust because their crawling, playing, and hand-to-mouth activities puts them in close proximity to surface dust. In addition, toddlers often directly ingest soil, and some ingest it on a regular basis (i.e., pica behavior).

Infants and children are particularly vulnerable to exposures to metals through the surface dust pathway because their crawling and play activity puts them in close proximity to surface dust and because they often mouth their hands (e.g., finger sucking) and objects in their environment. This results in intakes of surface dust that are generally greater than those normally found in adults (e.g., Barnes, 1990).

Metal migration is highly dependent on soil properties, the particular metal of concern, and metal speciation (see Section 3.1.5.). Thus, the concentrations of metal contaminants in soil can be expected to vary with depth as well as with the size of metal-bearing particles. For example, higher concentrations of lead and smaller particle sizes are found near the soil surface (Duggan and Inskip, 1985; Duggan et al., 1985; Fergusson and Ryan, 1984; see Chaney et al., 1988, for review). Bioavailability of lead for both inhalation and ingestion exposure routes increases with decreasing particle size (Barltrop and Meek, 1979). The depth of soil that an

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individual may be exposed to will depend on the individual's activities. Therefore, site-specific exposure assessments must measure soil metal concentrations at the depth appropriate to the metal(s) of concern and human receptor behaviors.

Livestock grazing in metal-contaminated areas take up metals from soils, plants, or air and move the metals into the human food chain. Metals that migrate into surface water and sediments are taken up by fish, shellfish, or other aquatic species that are then consumed by humans. Further information about movement of metals from soils or waters into the food chain is found below in the discussion of ecological pathways (Section 3.4).

3.2.2.2.1. Application

Dietary pathway: There are two approaches to assessing exposure through the dietary pathway. One way is to conduct a food monitoring survey to measure concentrations of metals in individual foods. Examples of surveys that can used in this context are found in DHHS (1996), Egan et al. (2002), O'Rourke et al. (1999), Scanlon et al. (2001), and Thomas et al. (1999). This information is then coupled with data about food consumption rates for each major food group. Consumption rates include the amount of food that is eaten and the length of time that exposure is expected to occur. General food consumption rates can be found in U.S. EPA (1997).

> Two approaches for assessing potential human dietary exposures to metals are through (1) the conduct of food monitoring surveys to measure concentrations of metals in individual food items, and (2) the use of biomarker measurements.

For site-specific assessments, surveys of actual consumption can be conducted. This is particularly valuable when conducting assessments of risks to subsistence farmers or anglers or ethnic populations whose dietary habits differ significantly from those of the general population. A second approach is to measure concentrations of metals in urine and feces or other biological tissues with known associations to ingestion rates (Clayton et al., 1999, 2002; Choudhury et al., 2001). This approach is valuable for site-specific assessments because it provides a direct measure of individual exposure rates.

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The second approach to estimating dietary exposures is the use of biomarker measurements. Because metals are not efficiently absorbed from the GI tract, significant amounts are excreted in the feces (see Section 3.3 Human Health Effects). Other metals (e.g., cadmium) may be excreted in urine subsequent to absorption and mobilization. Multiplying the metal mass in feces (concentration × amount per unit time) by percent bioavailability will provide an estimate of metal ingestion rates. Metals can be measured in other tissues as well (e.g., lead in bone or hair); the results are indicative of past exposure but difficult to quantify in regard to route or amount.

Direct soil ingestion: Soil may be incidentally ingested when eating improperly washed fruits or vegetable or from swallowing inhaled dust. Children, especially toddlers, are also exposed through hand-to-mouth activity, putting dirty or other objects directly in their mouth (U.S. EPA, 2002). In addition, toddlers often directly ingest soil, and some ingest it on a regular basis (ingestion of soil at least twice a week for a month or longer is known as pica). There are four attributes to soil exposure estimates: the volume of soil (area × depth) to which an individual could be exposed (the "C" [concentration] term in risk equations), the potential duration of exposure, the amount of soil ingested, and the bioavailability of metal in soil).

The area of exposure is defined by general habits as well as the potential region where excess metals may have been deposited. The depth of soil that an individual may be exposed to will depend on the individual's activities. For children exposed to lead, mercury, or other similar neurotoxic metals, the default value for the C term is the average surface (usually 0 to 5 cm) concentration in a child's residential yard, and the time of exposure is the chronic average daily intake from 0 to 6 years of age, the period of neurotoxic vulnerability. Other metals will have different spatial averaging areas and depths and different averaging times, depending on the exposure scenario and window of vulnerability. As an example, cancer endpoints have chronic exposures averaged over adult lifetimes, whereas noncancer endpoints have subchronic exposures averaged for shorter durations of exposures related to shorter toxicological onsets.

Several studies have estimated the amount of soil ingested by children and adults (e.g., Binder et al., 1986; Calabrese et al., 1989, 1997; Clausing et al., 1987; Davis et al., 1990; see U.S. EPA, 2002a, for review). Estimates for children 2 to 6 years of age range from 39 to 271 mg/day; however, considerable uncertainty is associated with estimates derived from each study.

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Arsenic bioavailability has been estimated for various soil types (Freeman et al., 1995, 1993; Ng et al., 1998; Salocks et al., 1996), as has lead bioavailability for adults and children (LaVelle, et al., 1991; Drexler et al., 2003). See Sections 2.2 and 3.3 for further discussion of bioavailability issues.

3.2.2.2.2. Limitations

Dietary pathway: The primary limitation is that specific populations may have different dietary habits than those of the general population. Additionally, locally grown foods may contain more or less metals than those surveyed in the general market basket. Most surveys estimate short-term consumption (e.g., 1 to 3 days) and may not capture intra-individual variability that would affect long-term averages (e.g., http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm). Furthermore, food consumption patterns change over time; thus, patterns discerned at any given time may not accurately represent historical exposures. This becomes important in reconstructing doses associated with exposures to metals that have a long residence time in the body (e.g. lead, cadmium). Due to the lack of data reflecting long-term consumption behavior, risk assessors often use the short-term data as a surrogate when conducting exposure assessments, which adds considerable uncertainty to the exposure estimates. An additional challenge is the integration of data from separate surveys of metal residue and dietary habits (e.g., Tomerlin et al., 1997).

> A primary limitation in using results from food monitoring surveys to assess dietary exposures to metals is that these investigations may not consider sub-populations and their variable dietary habits.
>
> Biomarker approaches are currently limited by data gaps and uncertainties in dietary bioavailability estimates for most metals, except lead.

Use of the biomarker approach is limited because accurate estimates of dietary bioavailability are not available for most metals (with the exception of lead) (see Section 3.3. Human Health Effects). Comparison with concentrations of metals in tissues such as hair, bone, or muscle to toxic threshold levels is not possible because CBR concentrations have not been established for humans.

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Direct soil ingestion: The amount of soil ingested by children can be expected to vary with numerous factors, including age, activity patterns, and accessibility to soil and dust. Current estimates have been based on short-term measurements (e.g., days), which cannot be expected to capture intra-individual variability and may not reflect long-term trends. Furthermore, these estimates do not represent pica behavior, in which much higher amounts of soil may be ingested (Barltrop, 1966; Calabrese and Stanek, 1993). Studies conducted thus far also do not distinguish between the quantity of dust ingested and the quantity of soil ingested. This parameter is important in connecting measured soil metal concentrations with surface dust ingestion that occurs in the indoor and outdoor environment (U.S. EPA, 1994). Few studies of soil ingestion in adults have been conducted; however, the estimates support the general assumption that average daily soil ingestion rates of adults who do not participate in activities in which intensive exposure to surface dust and soil occur (e.g., occupational gardening, construction work) are lower than those of children (Calabrese et al., 1990; Hawley, 1985),

3.2.2.3. Water Pathway and Oral Exposure

Humans, unlike ecological receptors, are exposed to and consume water specifically treated for human consumption (i.e., drinking water). Treatment of ambient water for human consumption removes DOC and suspended organic sediments that can form complexes with metals. Thus, the exposure context of metals in human drinking water will be very different from that of ambient water. Inorganic forms of metals in drinking water will consist of the more bioavailable, water-soluble species. Treatment also removes bacteria that can participate in organification reactions of toxicological significance to humans (e.g., methylation of inorganic mercuric mercury). Metals can enter drinking water at various stages of treatment or delivery of the water. Distribution systems within homes (pipes, storage containers, etc.) and, in the case of lead, glassware, can contribute metals to the water (Graziano et al., 1996). Other exposure pathways from water are discussed in Newman et al. (2003).

People also can be exposed to metals dissolved in ambient surface water or in association with suspended sediments; the latter can serve as a long-term repository for waterborne metal particles. Such exposures occur during swimming or other recreational activities or during occupational activities in which the sediments are disturbed or resuspended in the water column.

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Children can be particularly vulnerable to exposure to sediment-borne metals as a result of swimming or play activities at or near the shoreline. Metal bioavailability in ambient surface water can be expected to be much more diverse than in treated drinking water or in groundwater because of the presence of organic carbon, inorganics, and suspended organic material that can serve as ligands or reactants for metals. Speciation will also vary with pH of the surface water.

3.2.2.3.1. Application

Estimation of intake of metals in drinking water requires information about concentrations of metals in the water and the amount of water consumed. Data on tap water consumption for the general population can be found in U.S. EPA (2000). Similar information on incidental ingestion of water during swimming, showering, and so on is not available.

> Exposure to inorganic metals in water results from drinking the water; dermal absorption during swimming or showering is a negligible exposure pathway and can be ignored.

3.2.2.3.2. Limitations

Generally, water metal concentrations are measured at the distribution point for municipal water delivery systems. The contribution of metals from pipes (either from the distribution system to the home or within the home) is rarely assessed. This can be highly variable, both within the system as well as temporally; water that remains in pipes overnight frequently has a higher metal load than water used during the day. Furthermore, water delivered from private wells directly to the home generally is not subject to treatment and may contain higher levels of organic carbon or other ligands to which metals can bind, thereby changing the bioavailability of the dissolved metals. Similar difficulties are encountered when estimating exposures from ambient surface waters. These factors can be incorporated into site-specific assessments, but local data will need to be collected on a case-by-case basis.

3.2.2.4. Transplacental Exposure

Maternal exposure can be important for establishing the body burden of certain metals prior to birth as a result of transplacental transfer or, during infancy, through breast milk (for

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organometallics only). Rapid changes during fetal development may result in critical windows of susceptibility to toxic effects. For metals that have long retention times in tissues, the maternal tissues serve as a reservoir for exposures to offspring long after cessation of maternal exposure. This can be a particularly important exposure pathway for metals that accumulate in the inorganic matrix of bone (e.g., lead, strontium, uranium) because as mobilization of bone minerals to develop the fetal skeleton results in transfer of maternal bone stores of metals to the fetus (e.g., Gulson et al., 1999a, b; Tolstykh et al., 1998).

3.2.2.4.1. Application

Transplacental exposures cannot be directly estimated from environmental measurements, and such assessments require the use of pharmacokinetics models. A few models of transplacental transfer of lead in humans have been developed (U.S. EPA, 1994, 1996; Leggett, 1993; O'Flaherty).

3.2.2.4.2. Limitations

The lead models for transplacental transfer rely on assumptions of a steady state between maternal and fetal PbB concentrations. This assumption will be violated if the mother is no longer exposed to lead, in which case fetal exposure is due to remobilization of lead from the mothers bones, which is likely to change during the time of pregnancy. Furthermore, if the mother experiences lead exposures for the first time during pregnancy, the lead will be partitioned among the various body compartments (bone, hair, blood, fetus) in a dynamic manner. Thus, the assumption of steady-state conditions in the model adds considerable uncertainty to the assessment. Nevertheless, use of the models is recommended, as they will provide a general estimate of potential risk. Similar models for other metals are not available, so quantitative estimates of fetal risk are not possible.

3.2.2.5. Integrated Exposure Models for Lead

Several models for simulating human exposures to specific metals are available. The IEUBK model for lead in children (U.S. EPA, 1994, 1996; White et al., 1998) was developed specifically for translating exposure measurements into risk estimates at sites contaminated with

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lead. Several studies offer comparisons between model predictions and observed blood lead (PbB) concentrations in children at particular exposure levels (Hogan et al., 1998; Bowers and Mattuck, 2001), and the model has had extensive application at lead-contaminated sites. A fully stochastic version of the exposure model in the IEUBK model that implements one- and two-dimensional Monte Carlo simulations of lead exposure is available, although it has had limited application in uncertainty analysis at lead-contaminated sites (Goodrum et al., 1996; Griffin et al., 1999). The IEUBK model and background documentation are available on line at http://www.epa.gov/superfund/programs/lead/ieubk.htm.

A stochastic human exposure model for lead that is linked to a lead pharmacokinetics model (O'Flaherty et al. 1995) has also been developed (Beck et al. 2001). Less complex models linking adult exposures and PbB concentrations are available as well (Bowers et al., 1994; Carlisle and Wade, 1992; Carlisle, 2000; Stern, 1994, 1996; U.S. EPA, 1996);

The IEUBK model standardizes exposure by assuming age-weighted parameters for intake of food, water, soil, and dust. The model simulates continual growth under constant exposure levels (on a year-to-year basis). The model also simulates lead uptake, distribution within the body, and elimination from the body.

> The **IEUBK model** is designed to predict the probable blood lead (PbB) concentrations for children between 6 months and 7 years of age who have been exposed to lead through environmental media (air, water, soil, dust, and diet).

3.2.2.5.1. Application

The IEUBK model has four functional components. The **exposure component** compares lead concentrations in environmental media with the amount of lead entering a child's body. It uses environmental media-specific consumption rates and lead concentrations to estimate media-specific lead intake rates. The **uptake component** compares lead intake into the lungs or digestive tract with the amount of lead absorbed into the child's blood. The **biokinetic component** shows the transfer of lead between blood and other body tissues or the elimination of lead from the body altogether. The **probability distribution component** shows the probability of a certain outcome (e.g., a PbB concentration greater than 10 μg Pb/dL in an exposed child, based on the parameters used in the model).

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The IEUBK model allows the user to input relevant absorption parameters (e.g., the fraction of lead absorbed from water) as well as intake and exposure rates. Using these inputs, the IEUBK model calculates and recalculates a complex set of equations to estimate the potential concentration of lead in the blood for a hypothetical child or a population of children (6 months to 7 years of age). The IEUBK model calculates the probability of a child having PbB concentrations greater than a certain level. (EPA's current risk goal is a probability of <5% of children with PbB concentrations at or above 10 μg Pb/dL.) By varying the data entered into the model, the user can evaluate how changes in environmental conditions may affect PbB levels in exposed children.

3.2.2.5.2. Limitations

The IEUBK model standardizes exposure by assuming age-weighted parameters for intake of food, water, soil, and dust. This adds some uncertainty to the results and may over- or underestimate exposures for particular individuals. Furthermore, the model does not predict an average PbB level for an entire community, as many input factors may vary between different homes within a single community. Instead of using community means for the environmental lead inputs, it would be more accurate to first apply the IEUBK model to individual homes or homogeneous areas and then combine the results in order to find the mean for a neighborhood or community.

An important consideration in studies of contaminated soils is to accurately define the "exposure unit," which involves the proper averaging area for the C term and the correct time frame for the IEUBK model. The default value for the C term is the average surface (usually 0 to 5 cm) concentration in a child's residential yard, and the time of exposure is the chronic average daily intake from 0 to 6 years of age, the period of neurotoxic vulnerability. Other metals will have different spatial averaging areas and depths and different averaging times, depending on the exposure scenario and window of vulnerability. As an example, cancer endpoints have chronic exposures averaged over adult lifetimes, whereas noncancer endpoints have subchronic exposures averaged for shorter durations of exposures related to shorter toxicological onsets.

3.2.2.6. Related Exposure Modeling Tools

A more generic exposure model, RESRAD, was developed by the U.S. Department of Energy for risk assessment of radionuclides (U.S. DOE/RESRAD; Yu et al. 1993, 1994; LePoire

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et al. 2000; http://www.dis.anl.gov/CEEESA/Waste_analysis_tools.html#Resrad). Although this model was developed for deriving surface radionuclide soil action levels, the extensive human exposure module is applicable to other metal contaminants. The model also includes functionality for Monte Carlo simulation.

Several efforts are underway to develop stochastic human exposure models that, although not specifically intended for assessing exposures to metals, would be applicable to such a endeavors. These include the EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model and Lifeline. The SHEDS model, developed by EPA's Office of Research and Development, National Exposure Research Laboratory, is a probabilistic, physically-based model that simulates aggregate human exposures and doses (i.e., via inhalation, dietary, dermal, and non-dietary routes) for population cohorts and multi-media, multipathway chemicals of interest (Zartarian et al., 2000a). A modified stand-alone version of SHEDS, called SHEDS-Wood, has been developed specifically for estimating exposures to wood preservatives (chromium and arsenic) (US EPA 2003a). This uses the same general approach as the aggregate SHEDS model, but focuses on children's exposure and absorbed dose to wood preservatives via the dermal and non-dietary ingestion routes. EPA has also developed a Dietary Exposure Potential Model (DEPM) that links national food consumption and chemical residue data to allow estimates of average dietary intakes of metals and other food contaminants (Tomerlin et al., 1997).

3.2.3. Routes of Exposure to Aquatic and Terrestrial Species

3.2.3.1. Aquatic Species

Potential exposure routes for aquatic species include inhalation/respiration, dermal absorption, and diet (either food or incidental sediment ingestion). The extent to which a metal is taken up by any one of these exposure routes is difficult to define for all relevant routes. Inhalation/respiration, which for aquatic species means general exchange across respiratory surfaces, can involve diverse gill and lung types.

> **Binding of metals to the gill surface** is the primary route of exposure for most water column organisms for short-duration exposures.

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Respiratory surfaces include fish gills, various molluscan and arthropod gill types, the pseudo-lungs of pulmonate gastropods, cells surrounding the sponge spongocoel, mammalian and avian lungs, and plant leaves. Absorption includes movement across the skin; the walls of such diverse structures as spongocoels, the cnidarian gastrovascular cavity, and the echinoderm water-vascular system; the filtration-based feeding structures of many crustacea, insects, and polychaetes; diverse phytoplankton cell membranes; and plant roots and leaves. Ingestion pathways can involve direct consumption or consumption after exchange through a trophic web. The diversity of potential receptors makes definition of exposure pathways more difficult for aquatic receptors than for humans.

The respiration/inhalation route is a particular challenge in aquatic exposure assessments because of the differing types of respiratory organs, the dynamic nature of the respiratory process in water, and the intimate contact between a receptor and metals dissolved in waters. Further complicating the issue, some respiratory organs can also be involved in locomotion, excretion, ion regulation, and food capture, sorting, and ingestion. The absorption route can involve uptake across a phytoplankton cell membrane, amphibian skin, arthropod exoskeleton, the general integument of an infaunal clam or annelid, or the egg membrane of a bird or amphibian. Absorption can occur from overlying or interstitial waters; these sources have very distinct chemistries that influence metal bioavailability.

Similarly, the ingestion route is difficult to define for aquatic receptors because of the diversity of feeding modes and food sources, such as sediments, suspended solids, microflora, animal tissues, and plant tissues. The combining of respiratory, locomotive, or feeding structures complicates description of the ingestion pathway for some species. The presence of life stages that feed differently also confounds exposure assessment.

Temporal aspects of exposure should be considered in assessments of any toxicant. Rapid speciation and phase changes associated with changes in pH/Eh make temporal issues particularly germane to metals. Fluctuating or pulsed exposures occur in situations such as snow melts, acidic precipitation

Temporal aspects of exposure are important considerations in assessing aquatic risks to metals. Sound risk analyses clearly articulate all assumptions about exposure durations.

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events, rapid changes in Eh/pH associated with photosynthesis and respiration, hypolimnetic discharge from stratified reservoirs, biocide (e.g., copper sulfate) spraying, and ingestion of prey items with seasonally high metal concentrations. Any risk assessment for metals must clearly state all assumption about duration of exposure.

***Water pathway and respiratory route*:** Binding of metals to the gill surface is the primary route of exposure for most water column organisms, at least for short-duration exposures. Chemical kinetics play an important role in this context, as gradients in pH and ionic composition exist at the gill surface microlayer due to respiration, excretion, and ion regulation. Dissolved aluminum toxicity to freshwater fish is a good illustration of this point (Playle and Wood, 1990). The deposition of aluminum on gills is determined largely by the rapid shift from dissolved ionic aluminum to an $Al(OH)_3$ precipitate on the gill surface due to the more alkaline state of gill microlayer water. How much aluminum speciation and phase association changes occur is a function of the initial pH of the bulk water. Exposure assessment should address metal speciation kinetics in such situations (see Section 3.1.4. Environmental Chemistry) or else inaccuracies will emerge in subsequent effects assessment.

> The FIAM states that, in general, metal ion availability and effect are correlated with free ion concentration or activity in the water. Consequently, knowledge of free ion concentration or activity is crucial to fully describing exposure. The FIAM is a powerful tool as long as it is applied with enough understanding to anticipate or recognize exceptions.

3.2.3.1.1. Application

Predicting exposure at the respiratory surface must include analysis of chemical speciation, chemical kinetics, and binding with biological ligands on the gill (or equivalent respiratory surface). The Free Ion Activity Model (FIAM) states that, in general, metal ion availability and effect are correlated with free ion concentration or activity in the water (Campbell, 1995; Brown and Markich, 2000). Consequently, knowledge of free ion concentration or activity is crucial to fully describing

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exposure. The Biotic Ligand Model (BLM) further suggests that the bioactivity of a metal is a result of its interaction with biological ligands (i.e., biological macromolecules on the surface of the respiratory organ) (see Section 3.4. Ecological Effects). It follows that a dissolved metal ion's bioactivity is a function of its complexation with dissolved ligands (which determines how much free ion will be available for binding with biological ligands) and the affinity and stability of the metal complexes with the biological ligands. Further complexation of metals takes place within the cells of the respiratory organ, with the remaining free metal available for binding to transport macromolecules for delivery to the organism's circulatory system; this results in the true delivered dose.

Equilibrium speciation can be used to estimate the aquatic free ion concentration and its resulting activity. In some cases, the free ion can be measured directly during an exposure assessment. Combining insights from the FIAM approach with those from the BLM and HSAB (see Section 3.1.2. Environmental Chemistry) theories allows general prediction of metal activity on biological surfaces as different as fish gills (Pagenkopf, 1983; Reid and McDonald, 1991; Janes and Playle, 1995), green algae (Crist et al., 1988; Parent and Campbell, 1994), and bacteria (Azenha et al., 1995). Entry across the integument could also be addressed with conceptual tools of the FIAM and BLM (Krantzberg and Stokes,1988), but this application is not yet sufficiently developed for immediate use.

In the absence of sufficient information about speciation, exposure concentrations for dissolved metals such as beryllium, cadmium, lead, and zinc can be normalized on the basis of water hardness. Most practitioners fit linear models (log of toxicity endpoint = log a + b [log of hardness] and back-transform them to produce a normalizing function:

$$\text{Toxic endpoint} = 10^{a}\,(\text{hardness})^{b}$$

This power function contains an easily corrected back-transformation bias that should be removed from predicted hardness-adjusted exposure concentrations (Newman, 1991). The use of hardness as a normalizing function should be done only when information on speciation is lacking, as there is greater uncertainty using this method.

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3.2.3.1.2. Limitations

The FIAM is a powerful tool as long as it is applied with enough understanding to anticipate or recognize exceptions. As examples of important exceptions, charged uranium complexes are toxic, in addition to the free ion (Markich et al., 2000), and the neutral mercury complex $HgCl_2^0$ is bioavailable due to its high lipophilicity (Simkiss, 1996).

The BLM has been parameterized for copper, nickel, silver, and zinc in fish and invertebrates (*Daphnia*). Some initial work has been completed for other species and metals, but rigorous parameterization/validation is limited to those organisms and metals listed above. Recent efforts in Europe have focused on extending BLM principles to describe chronic toxicity; the results should become available in the near future. At present, the BLM approach assumes that delivered dose is equivalent to the amount of metal bound to the gill (or other respiratory organ), which may overestimate exposure. Models needed to predict within-cell complexation of metals into available and nonavailable pools have not yet been developed.

3.2.3.2. Food Chain Pathway and Dietary Exposure

Defining the particulars of metal exposure by ingestion is complicated by the diversity of feeding modes, digestive systems, and physiology of candidate receptors. That diet borne exposure to metals can result in accumulation in aquatic organisms is well established, although the rate and magnitude varies among organisms. What is less well understood is how best to express dietary exposure in a way that can be linked to toxic effects. For nonionic organic chemicals, evidence is strong that whole-body burdens of chemical (normalized to lipid content) are robust metrics of toxicological dose, and these relationships appear to be independent of whether exposure was via water or diet. In fact, the greatest strength of the body residue approach for organic chemicals is that it effectively integrates different exposure pathways into a single expression of dose and toxicological potency.

> Currently, *no* standard approaches exist to assess diet borne exposures of metals to aquatic organisms in water quality assessments, and consequently, the most significant limitation involves a lack of broad understanding of the mechanisms underlying diet borne metal toxicity.

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For metals (aside from organo-selenium and methyl mercury), the situation is far more complex, and whole-body residue does not appear to be a robust indicator of dose when compared across a range of exposure scenarios and/or organisms. The reason that whole-body residue/effect relationships are not as effective for assessing metals probably stems from the fact that although distribution of nonpolar organic chemicals in organisms is influenced largely by passive partitioning, uptake, distribution, and disposition of metals is governed by a number of active biochemical processes. For example, some organisms take up metal and sequester it into "storage" compartments in chemical forms that have little toxicological potency, whereas other organisms actively excrete excess metals. Even for a particular organism, uptake and disposition of metal may vary between waterborne and dietborne exposure (e.g., Szebedinszky et al, 2001; Kamunde et al., 2002).

Even though these issues confound the development of simple dose/effect metrics based on whole-body metal residues, one must presume that residue/effect relationships could be established if there were better understanding of more specific concentration/response relationships for the site (or tissue) of toxic action. For example, some studies have suggested that the metal concentration in the cellular cytosol (as opposed to that bound to cell walls or sequestered in nonbioavailable metal granules) may provide a better expression of internal metal dose associated with toxic effects. Others have suggested that whole-body residue/effect relationships are confounded because the factor determining effects is not concentration per se, but rather the rate of metal uptake.

> Assessment of diet borne metal exposure is best considered in two contexts: (1) diet borne exposure leading to accumulation and exposure to higher levels in the food chain (e.g., humans, wildlife) and (2) diet borne exposure leading to direct effects on exposed organisms.

For these reasons, assessment of diet borne metal exposure must be considered in two contexts: (1) diet borne exposure leading to accumulation and exposure to higher levels in the food chain (e.g., humans, wildlife) and (2) diet borne exposure leading to direct effects on exposed organisms. For the former, the primary challenges are to predict the aggregate uptake of metal from both waterborne and diet borne exposure and to express that accumulation in terms

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that are appropriate to assessing risk to the consuming organisms. Issues that come into play in this scenario include whether forms of metal that are sequestered and detoxified by the aquatic organism are bioavailable to organisms that then consume those aquatic organisms. With respect to the second scenario, the literature is mixed on the degree to which this is an important pathway for inducing toxicity to aquatic organisms and how best to quantify exposure in that context.

3.2.3.2.1. Application

There currently are no standard approaches to assess diet borne exposures of metals to aquatic organisms in water quality assessments (Schlekat et al., 2001). For the organometallic compounds of organo-selenium and methyl mercury, diet borne exposure has been clearly shown to be a primary route of both uptake and toxic effects and must be considered in assessments of these metal compounds. Beyond those two compounds, the picture is much less clear. Toxicity to aquatic organisms from diet borne exposure to metals has been demonstrated where exposure is sufficiently high, although in some cases these concentrations are extreme (e.g., 10,000 µg/g Cu) (Handy et al., 19**). If the diet borne exposure necessary to elicit effects is exceptionally high, it is not clear that this pathway will drive ecological risk, as the environmental concentrations necessary to produce these exposures may be so extreme that ecological risk will occur via other pathways (e.g., direct toxicity of waterborne metal).

In other studies, however, effects from diet borne exposure have been demonstrated at relatively low exposure concentrations, such as in zooplankton studies (Hook and Fisher, 20**). This raises much greater concern for metals assessment because it raises the potential for toxicologically significant exposures occurring in cases where risk via a waterborne pathway is low. That potential notwithstanding, other studies evaluating diet borne exposure with the same organisms and metals but somewhat different methods have reached different conclusions regarding the significance of diet borne exposure (Metzler, 2003). Diet borne exposure to metals is an area of active research, and it is likely that new insights will be forthcoming to rationalize what now appear to be conflicting data into a more comprehensive understanding of diet borne metal effects. Until that time, the absence of a standard approach will require that decisions

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regarding the handling of diet borne metal exposure in aquatic assessments be made on a case-by-case basis.

Some bioaccumulation models for metals include consideration of diet borne exposure, although few, if any, link this accumulation directly to effects. Among metals for which little is known regarding trophic transfer, HSAB theory (see Section 3.1.2. Environmental Chemistry, HSAB for metal classes) may provide some basis for predicting the bioaccumulation potential of metals. Class B and intermediate metals have greater binding potential to algal components than do Class A metals (Reinfelder and Fisher, 1991); for this reason, Class B metals are more likely to bioaccumulate in the food web and result in higher exposures of aquatic organisms. See Section 3.2.1. for additional discussion of metal bioaccumulation models.

3.2.3.2.2. Limitations

As indicated above, the primary limitation in assessing diet borne metal exposure for aquatic organisms is the absence of a broad understanding of the mechanisms underlying diet borne metal toxicity and the consequent lack of a standard assessment approach. Establishing rigorous residue/effect relationships that integrate waterborne and dietborne metal exposure is a critical need. When assessing dietborne exposure through direct measurement from field samples, there are methodological issues to be resolved, such as whether to depurate the digestive system of prey organisms. Metal contained in food or sediment within the digestive system will increase measured body burdens, but it may not have the same biological availability as metal residing within organismal tissues (Chapman et al., 2003). Fractionating body burdens of metals (e.g., cytosolic metal vs. metal granules) has been suggested as a better means of identifying the most readily accumulated fraction of dietborne metal (Reinfelder, Fisher, Luoma ref**), although the interpretation of this information in the context of risk assessment has not been rigorously developed.

In cases where trophic relationships are not well understood, stable isotope techniques can aid in defining

> Not all benthic organisms are exposed to sediments. Some feed and respire in the overlying water column. Sediment exposure estimates apply only to those organisms that extract nutrients or oxygen from sediments and pore water.

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the trophic status of species of concern and can be used to delineate the food web (i.e., who is feeding on whom). The ^{15}N concentration increases relative to ^{14}N concentration with each trophic exchange, and statistical models can link trophic status to metal concentration (e.g., Cabana et al., 1994). Other uncertainties include how behavioral changes induced by dietborne metal exposure may affect the survival of the exposed organism (Baird ref**).

3.2.3.3. Sediment Exposure

Most situations involving dissolved metals can be addressed adequately by assuming near-equilibrium conditions between water and sediment concentrations (Hoffmann, 1981), as long as one is sufficiently aware that some conditions can lead to important nonequilibrium dynamics (Paquin et al., 2003). Bioavailability, sediment transport, and chemical speciation all affect exposure of benthic organisms to metals. Additional issues of trophic transfer and routes of exposure (gills or equivalent vs. dietary) need consideration in the same manner as discussed above for water column organisms.

There are two major approaches for assessing sediment exposure and subsequent effects: the EqP and SEM-AVS modifications to the EqP. Other minor approaches include sequential extractions with different media (water, weak acids, strong acids) or normalization to total iron or organic carbon. Each has its strengths and limitations. Detailed discussions are provided in Paquin et al. (2003) and Newman et al. (2003), with additional information provided in Section 3.4. Ecological Effects.

3.2.3.3.1. Application

Several approaches have been taken for estimating exposures to sediment-associated metals that account for bioavailability differences among various sediments. The EqP approach assumes that sediment organisms are exposed to metals in the pore water and that the pore water concentrations are a function of an equilibrium of metal between organic carbon (particles) and the water

> When the molar concentrations of *acid-volatile sulfide* (*AVS)* in sediment exceeds the amount of *simultaneously extracted metal* (*SEM*), the metals are expected to associate with the solid phase and not be bioavailable.

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phase. A first approximation of this partitioning can be done through application of the octonal-water partition coefficient (K_{ow}). Further, it can be assumed that the pore water will contain the same amount of dissolved metal as the overlying water column, and therefore exposure concentrations for sediment organisms can be estimated solely on the basis of water concentrations. However, it is known that this simplification, which was originally developed for neutral organic substances, has considerable inaccuracies when applied to metals (Paquin et al., 2003) and needs to be adjusted to account for sediment binding of metals by iron sulfides. This is accomplished by normalizing the amount of AVS (1 N HCl extractant) in sediment to the amount of SEM; when the molar concentration of AVS exceeds that of metals (SEM-AVS <0), then the metals are expected to associate with the solid phase rather than interstitial water. It is further assumed that this low activity of metals in interstitial water is indicative of low toxicity to benthic organisms (Di Toro et al., 1990). The use of this SEM-AVS as exposure estimates that are correlated with toxicity of metals in sediment has been explored closely for Class B or borderline Class B metals (Di Toro et al., 1990; Ankley et al., 1991; Carlson et al., 1991; Berry et al., 1996; Hansen et al., 1996; Ankley et al., 1996). See Section 3.4.x. Effects, Aquatic, Sediment for further discussion.

Although the correspondence of SEM-AVS to toxicity was found to be strong in these studies, the approach may not be applicable to all benthic organisms because of its reliance on the chemistry of bulk anoxic sediment; most organisms live in oxygenated burrows and/or ingest and reprocess sediment. A better understanding of the mechanisms of metal accumulation from sediment and their relationship to toxic effects is badly needed. Until such information becomes available, the SEM-AVS model can be used in exposure estimations as long as its shortcomings are acknowledged appropriately.

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Other tools for determining the exposure concentration of sediment-bound metals include metal concentrations in chemical (Tessier et al., 1984; Babukutty and Chacko, 1995; Fan and Wang, 2001), acid (Luoma and Bryan, 1978; Langston, 1980), or biomimetic (Chen and Mayer, 1998; Mayer et al., 2001; Weston and Maruya, 2002) extracts. However, no consensus yet exists on their best use for different types of metals or metalloids. Several other methods have been proposed. Based on the premise that iron oxides in oxic sediments lower metal bioavailability, iron in a 1 N HCl sediment extract has been used to normalize metal exposure concentrations (Luoma and Bryan, 1978). Increasing concentrations of organic carbon can decrease metal bioavailability (Crecelus et al., 1982), so normalization of sediment metal concentrations to organic carbon content has been useful in other cases. The more readily extracted metals from sequential chemical extraction schemes tend to be the most bioavailable (Tessier et al., 1984; Young and Harvey, 1991) and can be used as exposure metal concentrations.

> The following information would enhance exposure assessments for benthic organisms: (1) improved computational or analytical methods for analyzing distribution of metal among components of the sediments, (2) improved computational methods for assessing the influences of metal form in sediments on sediment-water metal exchange, and (3) a better understanding of the processes controlling bioaccumulation of metals from solution and food by metazoan species directly exposed to the sediments

3.2.3.3.2. Limitations

Exposure assessment for benthic receptors could be enhanced if a clearer consensus were reached about the utility of each of these methods for different classes of metals, biological species, and sediment types. Specifically, the following information is needed to improve exposure analysis: (1) improved computational or analytical methods for analyzing distribution of metal among components of the sediments, (2) improved computational methods for assessing the influences of metal form in sediments on sediment-water metal exchange, and (3) a better

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understanding of the processes controlling bioaccumulation of metals from solution and food by metazoan species directly exposed to the sediments (Luoma, 1989).

EPA (2002) published a report on the application of solid phase AVS equilibrium partitioning sediment benchmark (ESBs) and interstitial water ESB as no-effect guidelines; to predict sediments that are acceptable for the protection of benthic organisms. Details of the AVS-SEM method are discussed in Section 3.5 and the metals issue papers. The method has been applied to predict toxicity of metals in sediment for Class B or borderline Class B metals. An ESB based on the difference between the concentration of SEM and AVS is appropriate for protecting benthic organisms from the direct effects of sediment-associated metals, and not for estimating metal bioaccumulation. Chapman (2003) discusses limitations concerning the AVS-SEM approach. Most notably, this approach applies only to organisms whose exposure is through interstitial water and does not account for dietary exposure and associated incidental sediment ingestion. Normalization to organic carbon content, sediment grain size, or cation exchange capacity of sediments does not generally lead to understanding bioavailability, but it is sometimes used for decision making purposes. Extractions, AVS, or sequential extractions can establish useful correlations but not mechanistic insight about bioavailability. Fractions should be considered operationally defined and not strict measures of phase association. Biomimetic methods are simple, but generalizations about results are difficult to make. Consequently, results from such studies tend to have site-specific utility.

3.2.3.4. Terrestrial Species

Pathways of exposure for terrestrial organisms to metals include movement from soils through the food web, and to a lesser extent, air deposition either into soils or directly onto terrestrial receptors (e.g., plants).

Terrestrial wildlife, plants, and invertebrates accumulate metals from direct contact with soil or sediment, from ingestion of contaminated food (plants or other animals), and from incidental soil or sediment ingestion. A conceptual model for direct and indirect exposure of terrestrial receptors to metals in soil is presented in Figure 7. Pathways of exposure include movement from soils through the food web, and to a

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lesser extent, air deposition either into soils or directly onto terrestrial receptors (e.g., plants). Because of significant differences in exposure patterns, it is more convenient to discuss methods by receptor group (invertebrates, plants, wildlife) rather than by pathways or environmental compartments.

3.2.3.4.1. Soil invertebrates

The soil ecosystem includes a complex food web of soil invertebrates (both hard- and soft-bodied) that feed on each other, decaying plant material, and bacteria or fungi. For risk assessment purposes, however, exposure is described as a function of soil concentration rather than a detailed analysis of movement of metals through the food web. This is a reasonable approximation for soft-bodied invertebrates (e.g., earthworms) whose exposure is primarily through soil pore water (from both dermal absorption and soil ingestion) (Allen, 2002). There is more uncertainty in correlating soil concentrations with effects in hard-bodied invertebrates because they are primarily exposed through ingestion of food and incidental amounts of soil. Regardless, for all types of soil invertebrates, exposure estimates must account for differences in bioavailability among soil types, which include differential partitioning to soil particles and pore water, metal speciation, and aging. Each of these processes is discussed in detail is Section 3.x Biochemistry.

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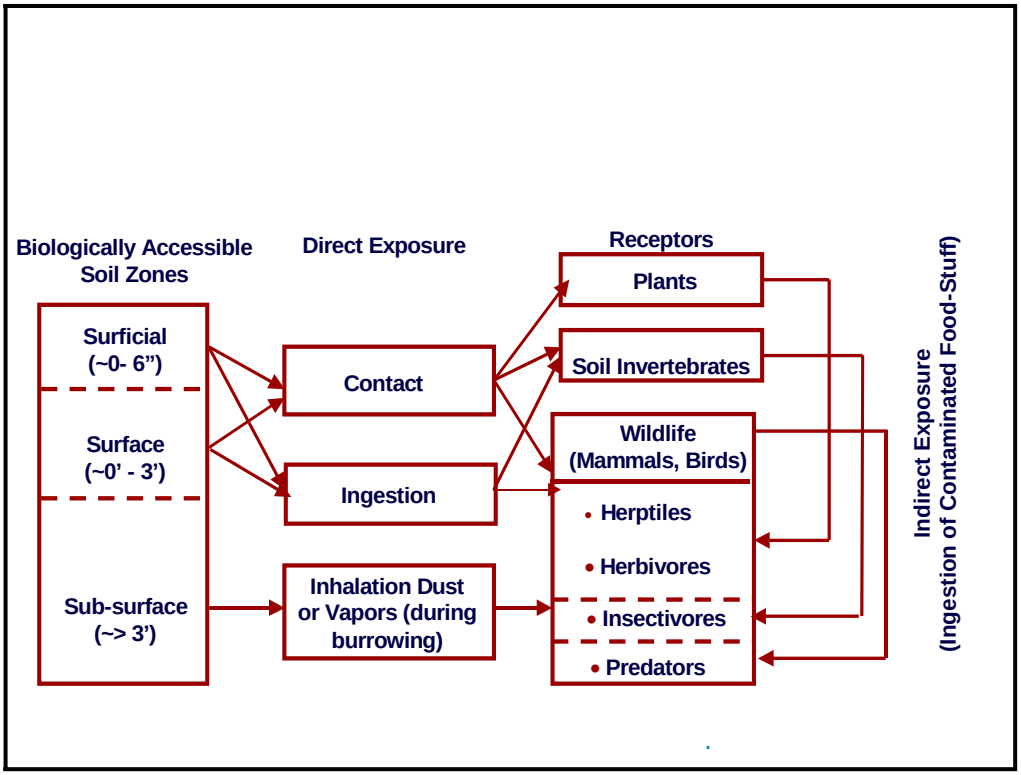

Figure 7. Conceptual model for direct and indirect exposure of ecological receptors to metals in soil zones

Source: Menzie and Little, 2000

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3.2.3.4.1.1. *Application*. Currently, soil invertebrate exposure is calculated on the basis of total metal concentration in bulk soils collected in the top 0–12 cm of soil (EPA, 1989). In higher-tier assessments, the organic matter on top of the soil (the "duff") may be analyzed separately to provide further detail on exposure to detritivores (such as *Collembola*) and deeper-soil-dwelling organisms (e.g., various species of earthworms). However, such measures of exposure are limited, as they do not account for differences among soils in bioavailability factors.

CEC recently has been shown as the most important factor modifying zinc bioavailability in soils for both invertebrates and plants, and it presumably will show a similar relationship for other cationic metals (Smolders, 2003 presentation in DC). Therefore, in addition to the concentration of metals in bulk soils, exposure estimates should include a measurement of CEC. Exposure measures in different soil types can then be normalized on the basis of relative CEC. However, comparison of field data with laboratory toxicity response information is best done through measuring metals in soil pore water from field assessments and spiked laboratory soils.

Soil chemical models are being developed to predict aging factors to modify bulk soil concentrations for the reduction in bioavailable fraction of metals over time (see Section 3.x.x. Biochemistry for a discussion of aging in soils). Preliminary studies suggest that consideration of aging may result in estimates of exposure from the bioavailable fraction as much as 0.1 X bulk soil concentrations. Until such time as the data become available for metals of concern, the European community has made a policy decision to apply an aging factor of 3 across all soil types, except when assessing acute (short-term) risks of spills (Smolders, E., presentation at EPA Public Hearing October 2003).

3.2.3.4.1.2. *Limitations*. Data on CEC for field soils are often available, but similar information from laboratory studies of the toxicity of metal-spiked soil is generally not available. Therefore, although exposure concentrations can be standardized across field locations, it is more difficult to make appropriate comparisons of field exposures with laboratory-generated concentrations-response functions. Furthermore, lab-to-field comparisons for exposure estimates are better correlated with concentrations of metals in pore waters. Such information is not available in the published literature and, therefore, must be estimated using EqP theory (as with sediment pore

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water analysis). Published soil binding coefficients (K_ds) can be used, although these values are inherently uncertain as well (published value depends on derivation method, soil type, etc.).

3.2.3.4.2. Plants

Plants access metals through the pore water, although micorrhyzae and phytochelatins released by the route can significantly influence the microenvironment and change uptake rates of metals (e.g., through pH changes) (Arnold and Kapustka, 1993; Cress et al., 1979; Karunaratne et al., 1986). Furthermore, plants have both active and passive mechanisms for taking up or excluding metals, depending on internal concentrations and whether or not the metal is an essential micronutrient. Plants can be exposed to metals via aerial deposition onto leaf surfaces. Although this might provide an exposure route for herbivores, it is inconsequential to the plant because the metals cannot penetrate the waxy surface of leaves and generally will not be taken up through leaf stomata in significant quantities.

> The highest accumulation of metals in plants generally occurs in the roots.

3.2.3.4.2.1. *Application***.** A wide variety of plant species take up metals from soil through their roots via various mechanisms (Cataldo and Wildung, 1978; Raskin et al., 1994). The default approach to estimating exposure of plants to metal is measuring metal concentrations in bulk soil. However, as with soil invertebrates, this overestimates exposure because it does not account for differential bioavailability that results from complexation with organic ligands and aging. Soil pH, organic matter, cation exchange capacity, and percent organic matter are the most important variables influencing bioavailability (see Section 3.4. on Ecological Effects). However, CEC and clay content are not consistently reported in the literature and therefore cannot be used to define relative bioaccessability and toxicity of metals. General categories of uptake based on soil pH and organic matter are shown in Tables 17, 18, and 19 for ranges typically found in soils. It is very clear that strongly acidic soils increase plant uptake of Zn, Cd, Ni, Mn, and Co, and increase the potential for phytotoxicity from Cu, Zn, and Ni. Alkaline soil pH increases uptake of Mo and Se, while Pb and Cr are not absorbed to any significant extent at any pH (Chaney and Ryan, 1993). These are sufficient as a qualitative guide for assessors to use in identifying soils with increased (or decreased) metal bioavailability.

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3.2.3.4.2.2. *Limitations*. Qualitative relationships between soil chemistry and bioavailability are appropriate for national-scale application. However, for site-specific or metals-specific applications, quantitative methods are preferred. It has been suggested that only uncomplexed, free ionic species of cations can be taken up by roots, and this has been described using a FIAM similar to what has been used in aquatic systems (Lund, 1990; Parker and Pedler, 1997). Studies to generate models to predict free copper activity from total metal content, pH, and organic matter content (Sauve et al., 1995, 1997a, b; McBride et al., 1997), while for lead, empirical models were generated using only total metal levels and pH. However, exceptions to the free-ion model have been identified. Ionic or organometallic complexes that increase the total concentration of elements at the root surface have been correlated with increased uptake, either through disassociated ions or through uptake of intact complexes (McLaughlin et al., 1994: Parker et al., 2001). In addition, it is not clear how well plants can distinguish between ions of similar size and charge. Plant uptake of macronutrients is much better understood than is uptake of micronutrients or contaminants, with the primary work on uptake of micronutrients focusing on iron (Welch, 1995). Different mechanisms have been identified that control macronutrient uptake by plants, providing a means through which contaminants can enter root tissue.

3.2.3.4.3. Wildlife

Food and the incidental ingestion of soil are the two most important exposure pathways for terrestrial wildlife.

The relative importance of exposure pathways and routes varies by species of animal as well as by metal (U.S. EPA, 2003), although, in general, wildlife exposure is primarily through diet and incidental ingestion of soils or sediments. EPA (U.S. EPA, 2003) has concluded that there are certain chemicals and exposure situations for which inhalation or dermal pathways are important, but under most situations they can safely be considered insignificant contributors to total metal loads. Table 12 presents metal-specific information for evaluating exposure to wildlife species (Menzie-Cura and TN&A, 2000).

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Table 12. Source Categories of Metals for Six Sentinel Species (Herbivores, Carnivores, Vermivores) Based on Application of Food-Chain Models with Default Exposure Assumptions

Species	Contaminants Taken up Predominantly From Soil (>75%)	Contaminants Taken up From Both Soil and Food	Contaminants Taken up Predominantly From Food (>75%)
Meadow vole (herbivore)	Al, Co, Fe, Vn	Sb, Cr, Ag	As, Ba, Cd, Cu, Pb, Mn, Ni, Se, Zn
Mourning dove (herbivore)	Al, Sb, Co, Fe, Ag, Vn	As, Ba, Cr, Pb, Mn, Ni	Cd, Cu, Se, Zn
Long-tailed weasel (carnivore)	As, Ag	Al, Ba, Co	Cd, Cr, Cu, Fe, Pb, Ni, Se, Zn
Red-tailed hawk (carnivore)	Ag	Al, As, Ba, Co, Mn, Vn	Cd, Cr, Cu, Fe, Pb, Ni, Se, Zn
Short-tailed shrew (vermivore)	Al, Fe, Vn	As, Ba, Co	Cd, Cu, Pb, Mn, Se, Ag, Zn
Woodcock (vermivore)		Al, As, Ba, Co, Fe, Vn	Cd, Cu, Pb, Mn, Se, Ag, Zn

Wildlife food chain exposures for metals are controlled by bioavailability, bioaccessibility, and bioaccumulation. The availability of metals in soils depends on whether exposure occurs via pore water or other pathways external to the organisms. Bioaccessibility of metals to animals and plants that live on or in the soils can be influenced by a number of soil parameters, such as pH, CEC, and organic carbon. These soil factors tend to be less important for soils that are incidentally ingested by wildlife species. For further review of soil bioavailability factors that are important in wildlife exposure, see Section 3.4.6.3 Ecological Effects (Wildlife).

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3.2.3.4.3.1. *Application*. In the absence of site-specific information, the following generalizations can be used (TN&A and Menzie-Cura, 2000):

- Metals for which uptake into food (either plants or soil invertebrates) tends to be the most important route of exposure include cadmium, copper, lead, nickel, selenium, and zinc.

- Metals for which incidental soil ingestion (and some food uptake) tends to be the most important pathway include aluminum, iron, and vanadium.

- Incidental soil ingestion is a proportionally more important pathway for herbivores than for carnivores or invertevores.

- Uptake into soil invertebrates (e.g., earthworms) is a proportionally more important pathway for animals that feed on these organisms. (Note: This assessment reflects work done with earthworms and may not apply to hard-bodied soil invertebrates such as *Colembolla*.)

The relative importance of exposure pathways (soil vs. food chain) is dictated by the fraction of metal-contaminated soil in the diet and the amount of accumulation of metal in food items. Table 13 provides a simple scheme for judging the relative contribution of food and soil before accounting for bioavailability. The values in the table are the percent contribution of exposure associated with the incidental soil ingestion pathway. The highest values are in the lower left-hand side of the table. Incidental ingestion of soil becomes proportionally more important for exposure to wildlife when (1) the BAF from soil to food (e.g., to plants or soil invertebrates) is less than 1 and (2) the fraction of soil in the diet is greater than 1%. With respect to refinements of exposure estimates, an understanding of the bioavailability of metals in incidentally ingested soils would be most useful for the exposure combinations in the lower left-hand region of the table and would not be particularly useful for combinations in the upper right-hand region.

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3.2.3.4.3.2. *Limitations*. Experience at metals-contaminated sites indicates that the above generalizations must be viewed with caution. As site-specific information is acquired, the relative importance of pathways may change. For example, site-specific data may show that the accumulation of a chemical into plants or soil invertebrates is much lower than indicated by the default assumptions. In such cases, incidental ingestion of soil would become proportionally more important. The bioavailability of metals in incidentally ingested soil is also variable, as discussed later. Therefore, when the exposure is being driven by incidental ingestion, refinements of exposure estimates can benefit from a better understanding of bioavailability. Attention must be paid to the bioavailability of metals for which incidental soil ingestion is the predominant pathway and where ecological risk is indicated, although very little information is available on this for most wildlife species.

Table 13. Percent contribution of incidental soil ingestion to oral dose for wildlife at different soil ingestion rates and bioaccumulation factors and a bioavailability of 100 percent

	Bioaccumulation factor from soil to food organism			
Percent soil in diet	0.01	0.01	1	10
0.01	0.99%	0.099%	0.01%	0.001%
0.1	9.1%	0.99%	0.1%	0.01%
1	50%	5%	1%	0.1%
10	92%	52.6%	10%	1%

Extrapolation from models developed for estimation of bioavailability of metals in soils for incidental human exposures may not be broadly applicable to all wildlife species due to the influence of differences in digestive physiology and anatomy across the broad and diverse range of mammalian and avian species (Menzie-Cura and TN&A, 2000). For example, metals present in soils may be more or less bioavailable within the gut of an herbivore that relies on fermentation as compared to the simpler gut of a carnivore that is designed to break down proteins. These gut systems differ in chemistry (including pH) and residence time. However,

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thoughtful application of such information in at least a qualitative approach will address many of the uncertainties in metals risk assessments.

3.2.4. FOOD CHAIN MODELING FOR WILDLIFE

3.2.4.1. Application

Food chain modeling can be used to estimate the exposure of wildlife to metals based on ingestion of soil, food, and water. The basic format of the model is the same as that for organic substances and is shown in Figure 8; detailed explanations are available in several related documents (e.g., EcoSSLs, ECOFRAM, U.S. DOE (1994)). Measured, or predicted/estimated, concentrations of metals in soil, surface water, and food items can be used in the model, or concentrations in food can be modeled using trophic transfer factors. TRIM.FaTE (http://www.epa.gov/ttn/fera/human_apex.html can be used for modeling media concentrations of metals as a result of aerial deposition. Information on diet, foraging area, and the like is found in U.S. EPA (1993). The absorbed fraction variable accounts for differences in RBA, and is either 1 (default value) or an appropriate estimate. Note that there is no adjustment factor (RAF) included for food, because the default assumption is that 100% of the metal will be absorbed or assimilated from the diet, even though it is possible that only a fraction of metal in soil may actually be absorbed.

This approach is the same as that used in risk assessments or organic substances except when trophic transfer rates are used to model food concentrations only on the basis of soil measurements (rather than using direct measures of concentration of metals in food items), in which case metal-specific transfer rates are required. As with aquatic organisms, trophic transfer values for metals in terrestrial systems are an inverse function of soil concentrations. Therefore, it is inappropriate to use constants for this term. Sources, use, and limitations of function of soil where apparent uptake ratios are greater at the lowest and highest concentrations of metals in soils as compared with the middle concentrations of metals in soils and where tissue metal concentrations remain stable over a wide range of soil metal concentrations.

Sample et al. (1998a) developed uptake models to predict concentrations in earthworms from soil concentrations. These models can be used to estimate the exposure of both the worms

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themselves and for vermivorous wildlife (e.g., song birds, voles, and shrews). For selected metals (arsenic, cadmium, copper, mercury, manganese, lead, and zinc), the best estimate of tissue concentration in earthworms is a simple ln-ln regression. The addition of soil pH data to the regression model did not markedly improve fit. If soil calcium concentration is incorporated into the regression model, a better fit can be obtained for cadmium and lead but not for other metals. Tissue concentrations are inaccurately estimated for the transition metals nickel and chromium by both simple and multiple regression models. For general estimates, log-linear regression models may be used as bioaccumulation models for arsenic, cadmium, copper, mercury, manganese, lead, and zinc in earthworms.

There is no compilation of plant BSAFs, but U.S. EPA (2000) (EcoSSLs) provides some data on select metals. The highest accumulation of metals in plants occurs in the roots, although other parts of the plant also accumulate metals to varying degrees (Greszta, 1982; Mitrofanov,1993). With the exception of a few hyperaccumulator species, most plant species do not bioconcentrate metals (i.e., BAFs <1). Lead, arsenic, chromium, and cobalt are not taken up by plants in measurable quantities, and the small amount that is taken up is mostly confined to root tissues (Xu and Thornton, 1985; Chaney and Ryan, 1994; McGrath, 1995; Chaney et al., 2000). Thus, measurements of plant shoot concentrations would not be useful for wildlife risk assessments because consumption of contaminated plant material is not a relevant exposure pathway for higher organisms. In the case of selenium and molybdenum, uptake into the edible portion of plant tissues can be quite high but is generally not sufficient to cause plant toxicities (Foy et al., 1978; Bingham et al., 1986; McGrath, 1995).

Plants are quite sensitive to manganese and zinc and may die before achieving high levels. Plant zinc concentrations are also an effective measure of changes in bioaccessibility as a function of soil treatment with amendments, such that a reduction of plant tissue concentrations of zinc following an amendment is accepted as evidence of reduced environmental availability of the metal (Basta and Sloan, 1999; Brown et al., 2000).

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Oral Intake (mg/kg/day) =

$$\left[Soil_j \times P_s \times FIR \times AF_{js}\right] + \left[\sum_{I=1}^{N} B_i \times P_i \times FIR \times AF_{ij}\right] \times AUF + \left[Water_j \times WIR\right]$$

Where:

$Soil_j$ = concentration for contaminant (j) in soil (mg/kg dw)

P_s = soil ingestion rate (kg/kg-body weight/day, dw)

FIR = food ingestion rate (kg/kg-body weight/day, dw)

AF = absorbed fraction of contaminant (j) in biota type (i)

N = number of different types of biota in the diet

B_i = contaminant concentration in biota type (i) (mg/kg dw)

Note: ($Soil_j$ x T_{ij}) can be substituted for B_i where T_{ij} = soil-to-biota trophic transfer factor (TTF) [as dry weight to dry weight] for contaminant (j) and biota type (I)

P_i = proportion of biota type (i) in diet (unitless)

AUF = area use factor; proportion of available habitat for a wildlife species within the area of concern (%)

$Water_j$ = concentration for contaminant (j) in water (mg/mL)

WIR = Water ingestion rate (mL/kg/day)

Figure 8. Wildlife Oral Exposure Model

(CITATION)

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3.2.4.2. Limitations

A potential limitation of using either measured or modeled tissue metal accumulation levels is that the effects assessment requires the accumulation level to be related to a benchmark effect level. This can be problematic, especially when whole-body tissue levels are involved, because what really matters is the effective metal concentration at the site of action of toxicity. If the concentration at the proximate site of action of toxicity is proportional to the whole-body concentration, then this is a lesser concern. However, if the concentration at the site of action is not proportional to the whole-body concentrations, then direct measures of metal concentrations at the site of action is required, especially at higher assessment tiers.

A further complication associated with using total metal levels in tissues to predict effects is that the absolute level of metal accumulation is not as important as the rate of uptake (Roesijadi, 1992; Hook, 2001; Hook and Fisher, 2002). Uptake is believed to occur because of the ability of some organisms to sequester metals that enter the cell (e.g., by inducing the synthesis of metallothionein [MT] or granule formation). Adverse effects are avoided as long as the rate of metal uptake does not exceed the rate at which the organism is able to bind the metal, thereby preventing unacceptable increases in cytosolic levels of bioreactive forms of the metal. If the rate of uptake is too great, the complexation capacity of the binding ligand (e.g., MT) could be exceeded; cytosolic metal levels then become unacceptably high, and adverse effects could ensue. However, measures of uptake rates are not available, so static concentrations are used instead.

Measurement of the form of the metal that is present in a tissue may be a more predictable indicator of the potential for effects than is total metal concentration (Roesijadi, 1992; Mason and Jenkins, 1995). Metals also may be bound to organo-phosphorus granules that sequester the metal, thereby rendering them nonavailable to bind with other intracellular target enzymes (Coombs and George, 1978; George, 1982). Although there is a wealth of available data on measured total tissue levels of metals, there are little data on intracellular speciation or sequestration of the metals. Although models that can be used to perform this sort of evaluation are currently under development, the ability of such models to be used as a tool in exposure assessment remains to be demonstrated. Therefore, measurement of total metal in plant (or animal) tissue remains the accepted default approach.

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3.3. HUMAN HEALTH EFFECTS

Goyer et al. (2003) provide an overview of human health effects issues associated with exposure to metals. They identified several unique properties of metals in relation to their uptake, metabolism, and elimination:

- ❑ Metabolism generally is limited to oxidation state transitions and alkylation/dealkylation reactions.
- ❑ Metals are sequestered by binding to specific plasma or tissue proteins (intrinsically capacity limited) or in bone, hair, or other inert tissues.
- ❑ Metals are hydrophilic and are predominantly eliminated in urine and bile.
- ❑ Metals and their complexes often are ionized, with tissue uptake (i.e., membrane transport) being diffusion limited and more often using specialized transport processes.

They also stressed the classification of metals and emphasized the significance in terms of health between nutritionally essential metals, primarily toxic metals, and metals with carcinogenic potential. Separation of metals into these groups impacts all three of the EPA risk assessment scenarios. This section discusses topics where these unique properties of metals require that adjustments be made when conducting effects analysis in risk assessments.

A trace metal is considered ***essential*** if it is present in all healthy tissues of humans; its withdrawal from the body induces physiological, biochemical, and structural abnormalities; and its addition either reverses or prevents these abnormalities.

3.3.1. ESSENTIALITY

Seven metals are known to be nutritionally essential for humans, and four others have possible beneficial effects (Table 14); these are reviewed in

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detail in Goyer et al. (2003). The response of organisms to exposure to these metals is conceptualized as having three phases: the biologically active zone; the inactive zone (plateau); and the pharmacotoxicological action zone (the U-shaped, or inverted, dose-response curve) (Figure 9).

Table 14. Classification of metals based on characteristics of health effect

Nutritionally Essential Metals	Toxic Metals With Possible Beneficial Effects	Toxic Metals With no Known Beneficial Effects
Cobalt Chromium III 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

In recent years, understanding of the nutritional importance of trace metals has grown rapidly, mainly due to a better characterization of their biological functions. Essential trace elements create health problems if they are either deficient or present in excess. Copper deficiency anemia and iodine deficiency goitre in children are examples of deficiency syndromes. Generally, intake of zinc, copper, selenium, and the other required elements is sufficient in affluent populations to avoid such diseases. However, mild deficiencies may occur—often as a combination of several essential metals—that may be

> ***Homeostatic mechanisms*** regulate the uptake of essential metals from food and water and their subsequent distribution in the body by allowing enhanced absorption or excretion at low dietary intakes and diminished absorption/excretion with high dietary intakes. ***Dietary factors*** can also reduce essential metals uptake.

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indistinguishable from the pathophysiological effects of primary deficiency of a single metal. In environmental exposure scenarios, it is important to ascertain that the general population has adequate intake of all essential trace elements to meet daily requirements so as to not confound adverse health effects due to lack of intake with toxic responses to excessive levels.

Uptake of essential metals from food and water and their subsequent distribution in the body are regulated by homeostatic mechanisms that allow enhanced absorption or excretion at low dietary intakes and diminished absorption/excretion with high dietary intakes. Furthermore, dietary factors can reduce the uptake of essential metals. For example, high phytate levels in the diet complex with endogenous and exogenous zinc, thus preventing reabsorption and increasing zinc elimination. Specialized carrier proteins have been identified for metals that may originally have developed as a transfer mechanism for the essential elements but are also used to sequester or eliminate nonessential toxic metals. Examples include transferrin, which carries iron, cobalt, and zinc from uptake sites to various target organs, and metallothionein in renal tissues, which preferentially binds zinc and cadmium (see Goyer et al., 2003, for a more in-depth discussion of protein-metal interactions).

There are a variety of ways, however, in which homeostatic control mechanisms can be overwhelmed or circumvented, resulting in a toxic effect of the essential metal. Furthermore, the actions of metals on skin or pulmonary membranes are independent of homeostatic controls. For example, chromium salts can produce severe effects in the skin or respiratory tract mucosa, and inhalation of zinc oxide fumes can give rise to allergic responses resulting in metal fume fever at doses less than oral toxicity levels (CITATION).

Toxic effects of essential metals also may be a consequence of a blockage of the availability or activity of essential metals by competitive actions of toxic, nonessential metals. For example, lead blocks the utilization of iron in heme synthesis by inhibition of the enzyme ferrochelatase, and there is evidence that cadmium can block the entry of zinc into the fetus, thereby causing a variety of developmental defects in the newborn. Cadmium, lead, and mercury, in combinations or by themselves, may antagonize availability of zinc, copper, and selenium when these essential elements are present in marginal amounts in the diet. Alternatively, a competitive interaction between one or more essential metals can lead to toxic effects, such as copper toxicity being enhanced by reduced levels of molybdenum and vice versa. This is discussed further in Section 3.3.4.

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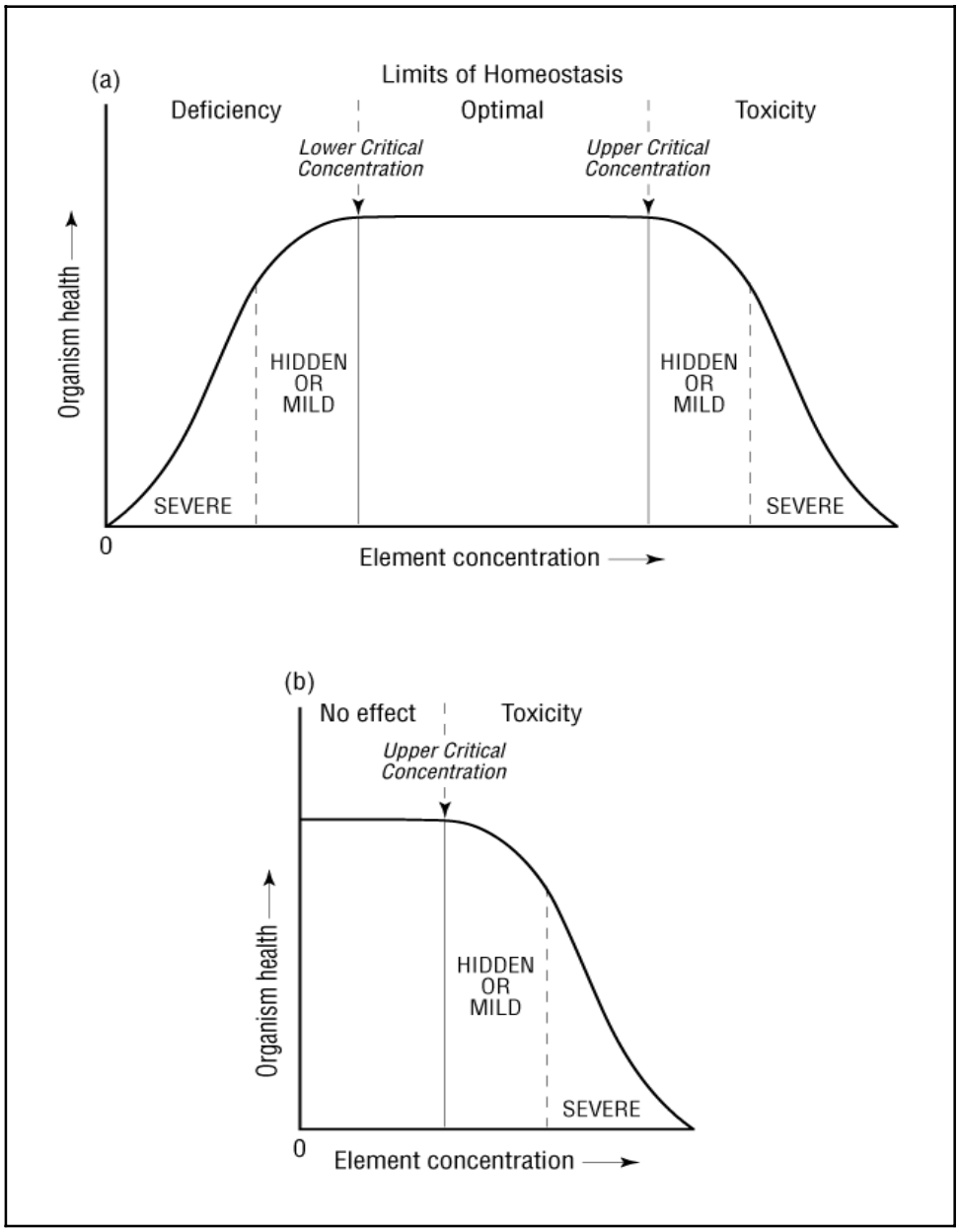

Figure 9. Dose-response curves for (a) essential elements and (b) nonessential elements (Alloway, 1995).

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3.3.1.1. Application

Considerable concern for human health has been focused on the nutritional aspects of essential metals. Because of this concern, the Food and Nutrition Board of the National Academy of Sciences has provided recommended dietary allowances (RDAs) for these metals and guidance for assessing risk from dietary exposures to these elements (NAS/IOM, 2001). The World Health Organization (WHO/IPCS, 2002) also has provided guidance on methods for assessing risks from excessive exposure to nutritionally essential metals.

> The ***recommended dietary allowance (RDA)*** is defined as the dietary level of intake of essential nutrients considered, on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons.

The RDA is dependent on several factors, such as bioavailability, age, gender, health status, and inter-individual variability. Bioavailability may depend on the form/species of the metal; the presence of phytates, which bind metals or substances such as ascorbic acid that facilitate absorption (iron); and the presence of toxic metals that may act as antagonists to the essential metals. It is important to recognize that the RDA is a public health concept based on the premise that if the requirement of each individual in a population is not known, the allowance must be high enough to meet the needs of those with the highest requirements. RDAs for essential nutrients cannot, therefore, be equated with average requirements; they must exceed the requirements of most of the members of the population group for whom the recommendation is made (NAS/IOM, 2003).

When conducting risk assessments for essential metals, the RfD should not be lower than the RDA. Generally, the benchmark dose (the dose that causes a toxic response in 10% of the organisms, using the upper confidence limit of the dose-response curve) is higher than the RDA, but the application of several orders-of-magnitude uncertainty factors can result in an RfD significantly below the amount required to avoid deficiency responses. Therefore, for essential elements, it is important to critically review the use of uncertainty factors (i.e., those applied for animal-to-human extrapolations or for acute-to-chronic concerns) and reduce them

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proportionately. Another approach is simply to state that the exposure should not exceed the RDA, although this does not account for the "inactive zone" in the U-shaped dose-response curve (Figure 9) (also termed the "margin of safety" between deficiency and toxic effects).

The term ***molecular*** or ***ionic mimicry*** has been applied to those situations in which a toxic metal forms a complex with an endogenous ligand, and the resulting compound mimics the behavior of a normal substrate, disrupting normal function. Such interactions could be considered in health assessments for exposure to specific metals. There is a large body of literature providing examples of molecular or ionic mimicry that includes most toxic metals (Clarkson, 1993; Ballatori, 2002). Most such examples involve essential and toxic metal interactions rather than toxic-toxic metal interactions and replacement of an essential metal with a nonessential or toxic metal. Thus, molecular or ionic mimicry may be viewed as a form of metal-metal interaction. One well-studied example is the replacement of zinc by lead in heme-synthesis, which inhibits the function of heme-synthesizing enzymes (Goyer and Clarkson, 2001).

3.3.1.2. Limitations

Although RDAs have been developed for all the essential metals, they are, out of necessity, set relatively high so as to be protective of all sensitive subpopulations. Should there be a narrow window between the required and toxic amounts of an element (e.g., as for selenium), then it is possible that sufficient amounts for those that need the most may be above the toxic levels of those that are most sensitive to the element. This potentiality must be evaluated on a case-by-case basis using what is known about potential sensitivities to that element. Furthermore, both RfDs and RDAs are set for individual metals and do not account for effects of mixtures.

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3.3.2. EVALUATING METALS BIOAVAILABILITY FOR HUMAN HEALTH RISK ASSESSMENT

3.3.2.1. Discussion

Evaluating bioavailability is important, because a given dose of a metal in an environmental medium may be absorbed to a different extent than the same dose administered in the study used to derive a toxicity value (e.g., oral RfD or cancer slope factor (CSF)). In addition, it is usually assumed that the bioavailability of all metal species is the same, regardless of exposure media. Studies clearly show that the bioavailability of metals does vary by environmental medium and the species present. Therefore, bioavailability information can significantly reduce uncertainty in risk assessments and more accurately characterize potential risks to exposed populations.

> Evaluating metals bioavailability can significantly reduce uncertainty in human health risk assessments and more accurately characterize potential risks to exposed populations.

The EPA Office of Solid Waste and Emergency Response (OSWER) has used bioavailability information in making quantitative adjustments. OSWER is responsible for administering the assessment and management of risks associated with hazardous sites listed on the National Priorities List as part of the Superfund program. In 1989, OSWER published a risk assessment guidance for use in human health risk assessments at Superfund sites and has updated this guidance periodically (U.S. EPA, 1989). This guidance recognizes that the toxicity of an ingested chemical depends on the degree to which it is absorbed from the gastrointestinal (GI) tract into the body. Thus, adjustments to bioavailability assumptions were developed to account for differences in absorption efficiencies between the medium of exposure and the medium from which the

> Estimating bioavailability of metals is complicated because it is dependent on many variables, including:
>
> ✓ Physical/chemical form of the metal
> ✓ Physical/chemical characteristics of the association between the metal and soil particles
> ✓ Particle size of metal species
> ✓ Metal source
> ✓ Weathering in soils

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toxicity value was derived. Further, because RfDs and CSFs are generally expressed in terms of administered dose rather than absorbed dose, it also discusses the need to adjust for differences in the expression of dose between the exposure and toxicity value (e.g., absorbed vs. administered dose). The Agency guidance recommends that the relative bioavailability adjustment (RBA) of a chemical should be assumed to be equal in food, water, and soil in the absence of adequate data to the contrary.

Estimating bioavailability of metals is particularly difficult because it is dependent on many variables, including the physical and chemical form of the metal, the physical and chemical characteristics of the association between the metal and soil particles, particle size of metal species, and the metal source. In addition, metal species continuously undergo reactions in soil, referred to as "aging or weathering," that affect bioavailability.

3.3.2.2. Current Practice

The Agency currently addresses bioavailability through the use of default values and, in some cases, through the development of site-specific and medium-specific values. To date, the most common 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 of the source used to derive the toxicity value (RfD or CSF). The RfD and CSF are typically developed from laboratory toxicity tests using highly bioavailable forms and are usually based on administered rather than absorbed doses. Thus, accounting for potential differences in absorption between different exposure media can be important in applications to site risk assessment (U.S. EPA, 1989). This is true for all chemicals, but it is of special importance for ingested metals because metals can exist in a variety of chemical and physical forms, and not all forms of a given metal are equally well absorbed. For example, a metal in contaminated soil may be absorbed to a lesser extent than when ingested in drinking water or food. Thus, if the RfD or CSF for a metal is based on studies using the metal administered in water or food, risks from ingestion of the metal in soil might be overestimated. Even a relatively small adjustment in bioavailability can have significant impacts on estimated risks and cleanup goals.

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When a reliable RBA value is available, the adjustment for the hazard quotient (HQ) takes the form, where HQ_{Adj} is the hazard quotient adjusted for RBA, RAF is the relative absorption factor, and DI is the daily oral intake (mg/kg/day).

$$HQ = \frac{DI}{RfD}$$

$$HQ_{Adj} = \frac{I \cdot RAF}{RfD}$$

Similarly, in estimating cancer risk (CR):

$$CR = DI \cdot CSF$$

$$CR_{Adj} = I \cdot RAF \cdot CSF$$

Similar adjustments can be made for the dermal and inhalation routes.

It is important to recognize that a default RBA value of 1 (100%) is not necessarily conservative (i.e., more protective of human health). The bioavailability of the metal in the exposure medium of concern at the site may actually be greater than in the exposure medium used in the critical toxicity study that formed the basis of the RfD or CSF. If this is the case, assuming RBA of 1 for the medium of concern would result in an underestimate of risk at the site.

As noted above, Superfund risk assessment guidance recommends that, in the absence of data to the contrary, the bioavailability of a chemical should be assumed to be equal in soil, diet, and water (U.S. EPA, 1989). However, the Agency recognizes that some cases may exist where sufficient data are available to support development of medium-specific default absorption factors for a particular chemical. The purpose of these medium-specific and chemical-specific

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default values is to increase the accuracy of exposure and risk calculations even when site-specific studies are not available.

Lead is an example of a chemical for which the Agency has established medium-specific default absorption factors for both children and adult populations. The IEUBK model for lead in children predicts PbB concentrations for a hypothetical child or population of children (birth to 84 months of age) resulting from exposure to environmental sources of lead, including soil, dust, air, drinking water, and diet (U.S. EPA, 1994a,b; White et al., 1998). An assumption in the model is that the ABA of lead in soil and dust, at low intake rates, is 0.3 (30%) and the ABA of soluble lead in water and food is 0.5 (50%). This corresponds to an ABA of 0.6 (60%) for lead in soil (or dust) compared to lead in water or food. The model also allows for the input of site-specific values.

The Agency has developed the Adult Lead Methodology (ALM) for assessing lead risks in adult populations (U.S. EPA, 1996a). An assumption in the ALM is that the ABA of lead in soil is 0.12 (12%). This value is based on assumptions that the ABA of soluble lead in water is 0.2 (20%) and that the RBA of lead in soil, compared to soluble lead, is 0.6 (60%).

The Agency has also derived RfDs that are specific for an exposure medium, based on consideration of bioavailability or other factors that might suggest unique dose-response relationships in that medium. For example, separate RfDs for cadmium in food and drinking water have been derived through the rationale that the bioavailability of cadmium in water is greater than that of cadmium in food by a factor of 2 (i.e., 5% vs. 2.5%, respectively [U.S. EPA, 2003a]). Similarly, the Agency recommends that a modifying factor of 3 be applied to the chronic oral RfD for manganese when the RfD is used to assess risks from drinking water or soil to account, in part, for potential differences in bioavailability of manganese in water and soil compared to that in food (U.S. EPA, 2003b).

However, even in cases where sufficient data exist to support default medium-specific absorption factors, site-specific studies may also be important. Important factors that can affect the bioavailability of metals in soil can be expected to vary from site to site or across the geography of a given site. These include the physical and chemical form of the metal and the

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physical and chemical characteristics of the association between the metal and soil particles. Default values for bioavailability may not accurately reflect these factors at any given site. Therefore, use of default values should not substitute for site-specific assessments of bioavailability, where such assessments are deemed feasible and valuable for improving the characterization of risk at the site.

3.3.2.3. Tools to Measure Bioavailability

As described in the NRC report (NAS, 2002), a variety of tools are available to attempt to measure bioavailability. The approaches include biomarkers of exposure (e.g., ALA activity from lead exposure), cell culture studies, isolated GI tract tissue, whole-animal approaches, and clinical studies. Of these options, the use of whole animals is most feasible (Weis and Lavelle, 1991); clinical studies offer desirable advantages but present many obstacles (Maddaloni et al., 1998). The following discussion focuses on the oral route of exposure.

> While a variety of tools are available to attempt measurement of bioavailability, the use of ***whole-animal approaches*** are the most feasible.

3.3.2.3.1. Animal Models

Historically, a variety of experimental animal models (in vivo) have been used to evaluate bioavailability, including rats, rabbits, monkeys, guinea pigs, and swine. Within an animal model, evaluation of bioavailability has included measuring the amount of metal in blood, body tissues, or excreta (e.g., feces and urine). The appropriate study design is dependent on the pharmacokinetics of the metal in the animal model and differences between the selected animal species and humans. In other words, it is important to consider how soluble forms of the metal are absorbed, how the metal is excreted, and whether there are any tissues where the metal might accumulate. The most common methods for measuring bioavailability in vivo are briefly discussed below.

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Blood measures. As generally described in the NRC report (NAS, 2002), the area under the concentration versus time curve is most often measured for GI absorption. Blood or plasma concentrations are plotted against time, and the area under the concentration versus time profile is calculated. In order to determine absolute oral bioavailability, the AUC following oral administration (AUC_{oral}) is compared with the AUC after intravenous administration (AUC_{iv}), the latter representing the AUC expected if the entire oral dose reaches the systemic circulation. The following equation represents the calculation of ABA ($F_{absolute}$) based on a single oral dose:

$$\text{Blood-derived oral ABA} = F_{absolute} = \frac{AUC_{oral} \ x \ D_{iv}}{AUC_{iv} \ x \ D_{oral}}$$

An analogous approach can be used to assess RBA by measuring the RAF. In this case, bioavailability under differing sets of conditions (e.g., oral bioavailability of a chemical from a soil matrix vs. from water) can be obtained from the ratio of the their AUCs, with one condition designated as the reference for comparison ("condition A" in the equation below).

$$\text{Blood-derived oral RBA} = \text{RAF} = F_{relative} = \frac{AUC_{(condition\ B)} \ x \ D_{condition\ A}}{AUC_{(condition\ A)} \ x \ D_{condition\ B}}$$

As with the measurement of ABA, doses of different sizes can be used, but only if they are in the linear (i.e., nonsaturable) pharmacokinetic range. In addition to providing information on the extent of absorption of chemical, blood, or plasma, data provide the best information on the rate of absorption. Although the method can theoretically be applied to virtually any chemical, this approach is best suited for chemicals eliminated from blood in a matter of hours to a few days. Also, reliable AUC measurements require several blood or plasma samples with chemical concentrations that are measurable. Animal subjects must be large enough to provide the number of samples and blood volume dictated by the experimental design and the sensitivity

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of available analytical methods. This limits the utility of small animals for these studies and often makes testing of environmentally relevant doses of chemicals difficult.

Urine measures: Many chemicals are excreted extensively in urine following their absorption, and analysis of the urine can provide an indication of absorbed dose. Typically, the animal subject is given a measured dose of the chemical, and urine is collected over time. The appropriate urine collection period depends on the elimination rate of the chemical but is usually extended until the chemical reaches undetectable or background concentration in urine. Based on the concentration of chemical in urine samples and their volumes, the cumulative amount excreted is calculated.

The oral ABA of a chemical can be calculated from the amount excreted following an oral dose ($A_{urine\text{-}oral}$) divided by the amount excreted after an intravenous dose ($A_{urine\text{-}iv}$). The intravenous dose is intended to represent the amount excreted in urine if the entire oral dose is absorbed. If doses of different sizes are used, the excreted amounts can be corrected for each dose if it is known or can be assumed that the amounts excreted are linearly related to dose.

$$\text{Urine-derived oral ABA} = F_{absolute} = \frac{A_{urine-oral} \times D_{iv}}{A_{urine-iv} \times D_{oral}}$$

Sometimes, urinary excretion data are used to draw inferences on ABA without benefit of a comparison with an intravenous dose. The amount excreted in urine provides an indication of absorbed dose only if other routes of excretion (e.g., biliary, pulmonary) are negligible, and elimination of the dose of chemical is complete. Because these conditions are rarely satisfied fully, bioavailability is usually underestimated by this method. Urinary excretion data can also be used to assess RBA by comparing the excreted amount under two different dosing conditions.

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$$\text{Urine-derived oral RBA} = \text{RAF} = F_{relative} = \frac{A_{urine(condition\ B)} \times D_{condition\ A}}{A_{urine(condition\ A)} \times D_{condition\ B}}$$

Fecal measures: Fecal excretion represents the inverse of oral bioavailability. A metal that is not absorbed following oral exposure will ultimately be excreted in feces. Therefore, measurement of fecal concentration can be used as an indication of the extent of absorption. Measurement of oral bioavailability involves collection of feces following single or multiple doses of the chemical. The collection interval must be sufficiently long to accommodate the GI transit of the dose. Also, some chemicals do not reach the systemic circulation but are instead excreted in the feces as the epithelial lining is sloughed into the lumen of the GI tract.

The collection of the unabsorbed dose must take into consideration the time course for these events. Absolute oral bioavailability can be estimated by comparing fecal excretion of the chemical following both oral and intravenous doses. The intravenous dose is important because it provides information on the extent of biliary excretion of the chemical and diffusion of the chemical from systemic circulation into the gut. Both contribute to chemical in the feces, but represent absorbed, rather than unabsorbed, chemical. If biliary excretion is known to be negligible, then fecal excretion data from oral dosing alone can be used to approximate oral bioavailability; however, if wrong, then the result will underestimate actual bioavailability.

$$\text{Fecal-derived oral ABA} = F_{absolute} = \frac{A_{feces-oral} - A_{feces-iv}}{D}$$

Tissue measures: Tissue concentrations can be used in combination with measurements of excreta to assess absorbed chemicals using a mass-balance approach. Such approaches require measuring the chemical in various tissues in the body to determine the total internal dose. Unabsorbed dose and the amount of dose excreted are also measured, such that the entire dose can be accounted for. From these measurements, the amount absorbed can be calculated.

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Measurement of absolute oral bioavailability can be accomplished without the need for a comparison intravenous dose, but the mass-balance approach is analytically intensive and obviously unsuitable for measurements in humans.

Alternatively, tissue concentrations alone can be used in some situations to assess oral bioavailability. This approach assumes that the concentration of chemical in tissues is directly proportional to the absorbed dose. It is best suited to measurement of RBA. The chemical can be administered to animal subjects in one or multiple doses. At specified times, animals are euthanized, and the concentration in one or more tissues is measured. Relative bioavailability is determined from the ratio of the tissue concentrations between the different types of oral doses—$C_{\text{tissue (condition A)}}$ and $C_{\text{tissue (condition B)}}$ in the equation below. If the oral doses compared are of different size, the tissue concentrations can be corrected for dose, provided that the relationship between dose and tissue concentration is linear.

$$\text{Tissue-derived oral RBA} = \text{RAF} = F_{\text{relative}} = \frac{C_{\text{tissue(condition B)}} \times D_{\text{condition A}}}{C_{\text{tissue(condition A)}} \times D_{\text{condition B}}}$$

The principal advantage of whole-animal oral chemical absorption studies is that they measure bioavailability in its most clinically relevant form, that is, from the GI tract and into the systemic circulation. This integrates all of the relevant biological components related to systemic absorption, including pre-systemic elimination, if present. By using the animals as surrogates for humans, these studies avoid the experimental and ethical problems associated with the use of human subjects. Currently, certain in vivo bioavailability studies conducted with an appropriate species are considered the gold standard for developing bioavailability information suitable for use in quantitative human health risk assessments, and they are often used to validate other bioavailability tools. For example, the young swine model for lead bioavailability has been used to validate in vitro extraction tests.

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3.3.2.3.1.1. *Animal Model Applications*. Animal models have served as the basis for making site-specific bioavailability adjustments at several Superfund sites. Scientists from EPA Region 8 sponsored the development of whole-body *in vivo* bioavailability studies in juvenile swine as a model of young children who were exposed to lead in soil contaminated with various forms of mine wastes (Lavelle et al., 1991; Weis et al., 1992, 1993). The results of these efforts were subjected to outside peer review and found to be valid and acceptable for use in adjusting the RBA for lead in human health risk assessments. As a result, the juvenile swine model is presently being used as the preferred animal model for lead (U.S. EPA, 1999). Site-specific bioavailability adjustments based on results from the juvenile swine model have been accomplished at several sites across the country, including the Murray Smelter in Colorado; Palmerton, PA; Jasper County, MO; Smuggler Mountain, CO; and the Kennecott site in Salt Lake City, UT.

> The ***juvenile swine model*** is presently being used as the preferred animal model by EPA for making site-specific bioavailability adjustments for humans exposed to lead in soil. Site-specific bioavailability adjustments based on successful application of the model have been accomplished at several sites across the US.

Interim draft guidance has also been developed by EPA Region 10 for making bioavailability adjustments with arsenic-contaminated soil (U.S. EPA, 2000). Recommendations are based on literature data on arsenic bioavailability and the results of a Region 10 animal study in which immature swine were dosed with arsenic-contaminated soil derived from the Ruston/North Tacoma Superfund site, which was a former smelter site (U.S. EPA, 1996b). This interim guidance recommends default values of RBA for arsenic in soil ranging from 60 to 100%, depending on the source of contamination (e.g., mineral processing, fossil fuel combustion, pesticides/wood treatment processes). As with lead, the juvenile swine is the recommended animal model for supporting departures from the default RBA assumptions.

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> Animal models are generally complex, time consuming, and more resource intensive than other tools, which may limit their feasibility to large sites where it is difficult to adequately characterize variability in bioavailability across the site.

3.3.2.3.1.2. *Animal Model Limitations*. Currently, bioavailability studies conducted with an appropriate animal species are considered the most reliable for making quantitative bioavailability adjustments in human health risk assessments. They are also used as a means to validate other tools, such as physiologically based extraction tests. However, animal models are generally complex, time consuming-, and much more expensive than other tools. As a result, use of animal models is usually limited to large sites where it is difficult to adequately characterize the variability in bioavailability across the site. An investigator must ensure that the study design and animal model selected are appropriate for the metal being tested. The best measure of bioavailability (blood vs. tissue vs. feces vs. urine) is dependent on the pharmacokinetics of a particular compound. As discussed above, each measure has its own inherent limitations. Further discussion of the limitations of animal models are discussed elsewhere (NAS, 2003; NEP, 2000; NFESC, 2000a, b).

3.3.2.3.2. *In vitro* Methods

Recently, significant effort has been expended on developing *in vitro* methods for assessing the RBA of metals, due to their ease of use and potential cost savings when compared against more traditional *in vivo* methods using laboratory animals. Several researchers have investigated *in vitro* models that attempt to simulate the conditions in the GI tract (Drexler et al., 2003; Medlin, 1997; Rodriquez et al., 1999; Ruby et al., 1993, 1996, 1999) and which are often referred to physiologically based extraction tests. These methods are based on the concept that the rate and/or extent of metals solubilization in GI fluid is likely to be an important determinant of metals bioavailability *in vivo*. These assays provide a measure of bioaccessibility or the amount solubilized in the GI fluid and available for potential absorption (Ruby et al., 1993).

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Model development has focused on the simulation of complex physiological and biological functions within the GI tract, including considerations of pH, solids:fluid ratios, motility/transit, and solution chemistry. The most common approach has been the two-solution method, which addresses pH changes in the GI tract by providing an exposure to both the low pH of the stomach (1.3 to 3) and the higher pH of the small intestine (5.5 to 7). Solution pH is usually maintained either by titrations with drop-wise addition of acid or base while solutions are continuously monitored or by using buffers.

The solids:fluid ratio used for *in vitro* models has ranged from 1:10 to approximately 1:150 (g/mL). None of these ratios reflects the 2:1 ratio observed in adults (3000 g daily food intake vs. the 1500 mL stomach volume) (Washington et al., 2001). It is recommended that this ratio be dictated by practical considerations. Therefore, a sample mass that can be accurately weighed and is representative should be provided, along with a volume that can help maintain good particle-to-solution contact and minimize any unusual kinetics.

Motility and transit time within the GI tract are difficult to model with standardization. Both processes vary greatly and can be affected by diet and daily cycles. Historically, investigators have used either diffusers, stirrers, or rotation devices to mimic these factors. All methods are adequate; however, the diffuser system is difficult to control and clean. Also, rotation mechanisms are not favorable to techniques that require constant pH monitoring.

Variations observed in extraction fluid chemistry are by far the greatest source of method deviations. Although most methods have the gastric solution dominated by HCl, other acids, proteins, and peptides have been added, with extraction times of about 1 hour. Intestinal solutions have their pH adjusted by addition of sodium bicarbonate and/or other biological salts and are extracted for 3 to 5 hours. Most systems were maintained at a temperature of 37 °C, and some methods have used argon to maintain anaerobic conditions, even though the GI tract is aerobic in humans.

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3.3.2.3.2.1. *Applications*. Physiologically based extraction tests have been conducted for a variety of metals, including lead, arsenic, cadmium, nickel, and mercury. Model results are currently being used as a screening tool only until adequate model validation has occurred. To date, EPA has not endorsed the use of *in vitro* techniques for making site-specific bioavailability adjustments.

> At this time, EPA does not endorse the use of *in vitro* methods for making site-specific bioavailability adjustments. Although *in vitro* methods are significantly cheaper and less time consuming than standard *in vivo* methods, the extraction techniques are based on the premise that solubility or bioaccessibility is the primary factor controlling bioavailability, which is not necessarily the case.

3.3.2.3.2.2. *Limitations*. In vitro methods are clearly significantly cheaper and less time consuming than standard *in vivo* studies. However, these extraction techniques are based on the premise that solubility or bioaccessibility is the primary factor controlling bioavailability, which is not necessarily the case. In addition, these tests cannot reflect the complex physiological or pharmacokinetic aspects of human absorption.

One of the key limitations of this approach is adeptly defined in NRC (2003):

> Regulatory acceptance of the tools used to generate bioavailability information in risk assessment is expected to be influenced by several factors, including the relevance of the tools to the site conditions and the extent of tool validation. Validation variously refers to the performance of a tool or approach in terms of reproducibility, reliability, and multi-lab calibration. An appropriate body of experimental work to validate a tool would (1) clarify where and when a tool yields a definitive response; (2) clarify that the tool can be linked to a biological response of a similar magnitude, and that the linkage stands up across a range of conditions in the type of environment that is being managed; (3) test the prediction of bioavailability using different types of experiments and field studies; (4) clarify which types of biological responses are best predicted by the approach; and (5) include critiques of the best applications and the limits of the tool,

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especially compared to alternatives. A tool that is well accepted and validated should be given greater weight than one that is new or experimental.

3.3.2.4. Next Steps

OSWER is currently developing a bioavailability document on metals to advise risk assessors and managers on whether to collect site-specific information on the bioavailability of metals in soil and how to evaluate bioavailability data for use in human health risk assessments. The document will outline a decision framework that explains how to use bioavailability data consistently as part of a human health risk assessment. The decision framework will consist of a two-tiered approach. The first tier presents general guidelines for determining whether bioavailability is worth considering at a particular site. This decision should be based in part on the potential for improving decision making at the site and whether the conditions represent a significant risk using default values for comparisons. The second tier involves an ordered process for the actual collection and analysis of bioavailability data. This tier will address method validation and site characterization procedures. The document also will include an evaluation of whether in vitro methods can be used in lieu of in vivo methods as the basis for making bioavailability adjustments for lead in soil and under what conditions the assay can be relied upon. The document is specifically limited to evaluating the bioavailability of metals in soil that humans may ingest. OSWER anticipates that it will be completed in early 2004.

3.3.3. CARCINOGENS

Metals are emerging as an important class of human carcinogens. At least five transition metals or metalloids—arsenic, cadmium, chromium VI, beryllium, and nickel—are accepted as human carcinogens in one form or another or via particular routes of exposure (NTP, 2002). Identification of the mechanism(s) responsible for metal carcinogenesis is elusive, partly due to the complex nature of metals interactions in biological systems. Many toxic metals, including carcinogenic metals, follow the metabolic pathways of similar essential metals. A major problem in recognizing metals as carcinogens in humans is the lack of populations of sufficient size and

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with definable single-metal exposure. The availability of a large Taiwanese population with defined exposure to arsenic in drinking water has provided sufficient data to establish a statistical link to the development of cancer in this population (NAS/NRC, 2001). Target organ sites for metals as carcinogens are summarized by Waalkes (1995).

It should be noted that essential metals can also be carcinogenic, although often the exposure routes are through injection rather than dietary routes. Chromium is often cited as an example of this duality. Chromium III is essential and chromium VI is carcinogenic. Zinc, copper, and iron have been shown to be carcinogenic in experimental animals under unusual circumstances of exposure, such as direct injection into the testis. Iron in combination with a carbohydrate produces tumors at the site of injection (Sunderman, 1978). Parenteral administration of iron in combination with nitrilotriacetic acid (an iron chelating agent) is a potent hepatocarcinogen; similar exposure to inorganic iron compounds is not carcinogenic (Cia et al., 1998). Although these observations may be dismissed as not relevant for health risk assessment for humans, they may be of concern for highly susceptible subpopulations (see section below). For example, persons with hemochromatosis (iron storage disease) develop hepatic cirrhosis and have a possible risk for hepatocarcinoma (NAS/IOM, 2003).

> EPA is currently revising its guidelines for conducting cancer risk assessment. These guidelines will be applicable to any metal or metalloid shown to be carcinogenic in humans. Currently, data and information on potential carcinogenesis for most metals is severely limited.

3.3.3.1. Application

Updated EPA guidelines for carcinogenic risk (U.S. EPA, 2003a, b) are presently in draft form under review. These guidelines will be applicable for any metal or metalloid that has definitively been shown to be carcinogenic. Currently, they are limited to arsenic (through drinking water exposure), cadmium, chromium VI (due to injections), beryllium, and nickel (from pulmonary or, in some cases, dermal exposures). Specific organ carcinogenesis for metals is reviewed by Waalkes (1995).

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3.3.3.2. Limitations

The information on potential carcinogenesis for most metals is severely limited. Epidemiological studies are lacking, and laboratory tests tend to demonstrate carcinogenicity only by artificial exposure routes (e.g., injection directly into the target organ). Furthermore, it is not known how metal-metal interactions may affect potential carcenogenicity. Therefore, at this time, most metals cannot be assessed for carcinogenicity risks in humans.

3.3.4. MIXTURES

Toxic metals are normally found in the environment as mixtures. That is, more than one metal is present at all times. Risk, therefore, may be mitigated or enhanced by the concurrent interactions of the various substances. There are generally three classes of interactions between metals: 1) between essential metals; 2) between toxic metals; and 3) between essential and toxic metals. Interactions between essential metals is related to maintaining optimal nutritional levels by synergisms and antagonisms at both physiological and extrinsic (dietary) sites. The WHO has summarized these interactions (WHO, 1996c). Examples of metals or metal compounds that reduce dietary uptake of other metals include iron oxalates, copper sulfides, trace element silicates, and phytates associated with calcium.

Although studies of populations around mining and smeltering operations are available (e.g., ATSDR, 1995), they generally do not explore the issue of exposure to metal mixtures (Sheldrake and Stifelman, 2003; von Lindern et al., 2003). In general, human health studies address blood lead (PbB) levels in children and urinary cadmium excretion in adults (ID Dept. of Health and Welfare Div. of Health, 2000), but they do not address potential interactions among the studied components (such as Cd, Pb, Zn, and Cu).

Studies of mixtures of greater than two metals are even less frequent than those for binary mixtures. Results from a ternary mixture of Cd, Pb, and Zn study in rats (Thawley et al., 1977) indicated slightly more marked adverse hematological effects in ternary mixtures exposure than in binary mixtures exposure. In another study (Fowler and Mahaffey, 1978), a relatively wide

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range of endpoints were investigated in a series of studies of each metal (As, Pb, Cd, Zn) singly and all possible binary and ternary mixtures. Body weight gain was depressed equally by the ternary mixture and the Cd-Pb mixture and, to a lesser extent, by the As-Pb and Cd-Pb mixtures, whereas food utilization was depressed to a greater extent by the ternary and As-Cd mixtures than by the other binary mixtures. In general, the biological parameters studied in this report indicated changes of smaller magnitude and inconsistency in direction when binary mixtures were compared with ternary mixtures. Unfortunately, these data are not adequate for predicting the magnitude of interactions. For some endpoints, the data are not available to determine whether the joint action will be additive, greater than additive, or less than additive or whether there would even be any joint action.

Toxic elements are normally found in the environment and, unless the exposure is overwhelming, their potential toxicity is antagonized by essential nutrients found in the diet. For example, fish contaminated with both mercury and selenium have less effect on human health than fish with each metal alone because these two metals will counteract each other. Cadmium toxicity from fruits and vegetables grown in contaminated soils may be mitigated by the zinc that is naturally found in nuts. Toxicity (or deficiency) also depends to a great extent on absorption and retention of a metal. In the case of copper, for example, zinc, sulfur, or iron play significant roles in modulating effects of deficiency or toxicity (Suttle and Mills, 1966).

3.3.4.1. Application

In the few instances where empirical data on effects of metals mixtures are available (see above discussion and associated references), the assessment should be conducted on the basis of information about the toxic threshold of the mixture or an adjustment to the threshold of the most toxic substance that is either ameliorated or made more severe by the presence of other metals.

> Empirical data on the effects of metals mixture are rare and available in only a few instances. In the absence of data for a mixed exposure scenario, at present, the default approach is to assume dose additivity for the individual components.

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In the absence of interaction data for a mixed exposure to metals, the default approach is to assume dose additivity for individual components (U.S. EPA, 1989). This approach is most appropriate for chemicals that produce the same effects by similar modes of action. However, Superfund guidance states that a strong case is required to indicate that two chemicals that produce adverse effects on the same organ system, although by different mechanism, should not be treated as dose additive (U.S. EPA, 1989). In the case of chemicals with different critical effects, separate effect-specific hazard indexes are estimated for each critical effect using the RfD for each metal.

Another potentially promising approach for mixture components with interactions data is the weight-of-evidence (WOE) approach for adjusting the hazard index, called the interaction-based hazard index (Hertzberg et al., 1999, U.S. EPA, 2000). For example, copper hepatotoxicity is assessed using the hazard quotient for copper and applying the qualitative WOE method to assess the potential impact of other metals on copper's hepatotoxicity. The hazard index for each metal is quantitatively adjusted for interactions on the basis of binary combinations of metals. For those where the sign of the interaction is known (e.g., additive or antagonistic) but the magnitude is not, a default value in the range of 5 to 10 could be used. It is recommended that if only one or none of the metals has a hazard quotient that equals or exceeds 0.1, then no further assessment for joint toxic action is needed, because additivity and/or interactions are unlikely to result in significant health hazard. Additional details of the guidance for complex mixtures can be found in U.S. EPA (1989, 2000) and Hertzberg et al. (2002).

Firmly established biomarkers of exposure can also be used to assess exposure models by comparing the predicted model results with those observed in the population studied. Choudhury et al. (2001) used urinary cadmium as a biomarker of exposure to evaluate a cadmium dietary exposure model linked to a biokinetic model. The predicted urinary cadmium and kidney cadmium burden levels of the model were in general agreement with those observed from human populations exposed to mixtures. More accurate model predictions of metal levels in tissue or fluids (i.e., biomarkers of exposure) may be obtained by linking exposure models with

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physiologically based pharmacokinetic (PBPK) models (Andersen, 1995; Clewell, 1995; O'Flaherty, 1998).

EPA guidance on human health risk assessments for chemical mixtures (U.S. EPA, 2000b) suggests that the selection of the assessment method begin with an assessment of data quality. A flow chart is provided that distinguishes between whole-mixture and component data and provides choices to characterize the similarity of the mixture or the components. Additional tables and text provide criteria and examples that illustrate these choices for a variety of data sets and assessment purposes. The discussion of key concepts (i.e., toxicologic similarity, similarity of action, and additivity for exposures or responses) and the data quality assessment scheme readily apply to both human health and ecological risk and hazard assessments for mixtures of metals and metalloids.

The Chemical Mixtures Research program at the Agency for Toxic Substances and Disease Registry is developing toxicological profiles and guidance for assessing the joint toxic action of chemical mixtures frequently encountered at hazardous waste sites. These guidance documents (available on the web at <http://www.atsdr.cdc.gov/interactionprofiles/ipga.html>) evaluate the strength of the data, likely routes of exposure, and adverse effects from individual components and the joint action of the mixture. These are exposure-based assessments for human health. They rely on robust data for environmental concentrations (particularly in soil), joint action models to describe the environmental fate and speciation of the components, and PBPK models. They also describe approaches using hazard quotient and WOE to estimate target organ toxicity doses (TTDs) for chronic oral exposures to components of the mixtures. The guidance describes approaches for modifying the TTD and for characterizing the level of confidence in the WOE determination for the endpoints from the mixture.

3.3.4.2. Limitations

The ideal basis for assessment of toxicity of environmental mixture(s) of metals (both from natural sources as well as anthropogenically enriched mechanisms) would be data and models of joint toxic action of the complete mixture or validated PBPK or physiologically based

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pharmacodynamic (PBPD) models (see Section 3.3.7) that would support prediction of the effects of different doses and proportions of mixture components. However, no PBPK models on complex mixtures of metals are currently available for use in risk assessment.

3.3.5. DELAYED EFFECTS

> ***Delayed toxicity*** is the occurrence of toxic effects after a prolonged interval has elapsed between cessation of external exposure to the chemical and the onset of the toxicity.

Delayed toxicity is different from acute toxicity or chronic toxicity. In some cases, chronic toxicity is the result of a gradual accumulation of the toxicant (i.e., the parent chemical or a bioactivated metabolite thereof) at its site of toxic action to a level sufficient to cause the toxic effect. This level is often referred to as a threshold level, and the toxic effect is often said to be a "threshold effect." The chronic nephrotoxicity caused by cadmium, for example, is believed to result from its accumulation in the kidney; toxicity occurs once a certain amount of cadmium has accumulated (Goyer and, Clarkson, 2001). The toxicity of cadmium to the kidney is therefore best characterized as a chronic toxic effect and as a threshold effect. In other cases, chronic toxicity is the result of continual low-level cellular damage that eventually becomes extensive enough to result in significant tissue or organ damage and accompanying loss of function.

> ***Acute toxic effects*** are effects that usually develop immediately or within a short period of time following an exposure of short duration and generally do not persist for extended periods or cause additional adverse effects over time. ***Chronic toxic effects*** are effects that generally occur following continuous or frequently recurring exposures and that persist for an extended period.

The salient characteristic that distinguishes delayed toxic effects from acute or chronic toxic effects is that with delayed toxic effects there is a lag period from the time that external exposure has ceased until the onset of toxicity. Delayed toxic effects may occur from single

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external exposures or external exposures of longer duration. Certain metals are known to cause—or are highly suspected of causing—delayed toxicity. A well-known example is the generalized pulmonary fibrosis caused by inhalation of poorly soluble beryllium salts (Becklage, 1979; Jameson, 1996, USEPA IRIS). This beryllium-induced illness is also referred to as delayed chemical pneumonitis or chronic beryllium disease. There is often a very long latency period, in some cases 30 years or longer, from cessation of exposure to the onset of symptoms (Becklage, 1979). This condition has been observed in people who during World War II worked in or lived near facilities that manufactured fluorescent lamps that contained beryllium. In many of these patients the condition became apparent only decades after exposure occurred. Beryllium has been isolated from the lungs of these patients.

Lead is another example of a metal that causes serious toxic effects. It is well documented that acute, short-term, or long-term exposure of humans to lead can result in neurological, neurobehavioral, developmental, and renal toxicity. In addition, lead may cause delayed toxicity due to its unique pharmacokinetic properties in humans and the clinical status of the human subject. Many studies of the pharmacokinetics of lead in humans show, or at least indicate, that (1) lead is absorbed by humans, (2) a significant portion of the quantity that is absorbed accumulates within the skeleton, (3) lead can remain in bone for many years, (4) chronic exposure to low levels of lead from environmental sources results in a continual build-up (accumulation) of lead in the human body and that this build-up is likely to continue for several years, and (5) lead that has accumulated in bone can later be resorbed from the bone, especially during periods of increased bone mineral loss (e.g., during pregnancy, breast feeding, menopause, old age), enter the systemic circulation, and partition to organs and other tissues to which lead is toxic. This latter scenario is particularly likely to occur when the individual has an increased demand for calcium (e.g., during pregnancy).

Toxicity of lead to humans does not require prior accumulation of lead in the skeleton, and lead that has accumulated in the human skeleton does not, while stored in the skeleton, cause toxicity. The significance of accumulation of lead in the skeleton from a human health perspective is that it can serve as an endogenous (or internal) source of exposure to lead later in

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life or, in the case of pregnant or nursing females who have previously accumulated lead, to the fetus or nursing infant (human subpopulations that are especially sensitive to the toxicity of lead). During menopause, for example, the rate of bone resorption (calcium mobilization from the bone to the blood) exceeds the rate of bone formation, and lead that is stored in the bone from exposures that took place years earlier can be released into the systemic circulation. Some investigators have stated that the mobilization of lead from the bone in menopausal women may contribute to the occurrence of neuropsychological dysfunction during menopause (Silbergeld et al., 1988). A relationship between PbB level and systolic and diastolic hypertension has been reported in postmenopausal women (Nash et al., 2003).

3.3.5.1. Application

When evaluating the hazards that a chemical substance may pose to human health, the Agency considers the toxic effects known or believed to be caused by the chemical, the routes of exposure from which these effects occur, and the levels and durations of exposure to the chemical associated with causing these effects. This information is usually derived from studies conducted in laboratory animals or from human epidemiologic studies. To assess the likelihood that any of the toxic effects caused by the chemical will occur in exposed individuals (i.e., the risk the chemical poses to human health), the hazard information is compared with the sources, routes, levels, and durations of exposure that are known or are believed to occur from the environmental releases that result from the manufacture, processing, use, and waste management (e.g., disposal, treatment) of the chemical. The assessment of toxicity is often divided into subassessments of acute toxicity and chronic toxicity, with emphasis on specific endpoints that provide information about reproductive, developmental, neurological, or carcinogenic effects.

Only one program within EPA, at the Office of Pesticide Programs (OPP), intentionally looks for evidence that a chemical causes delayed effects, and that program is confined only to hazard assessments of organophosphorus (OP) pesticides, specifically, the potential for these substances to cause delayed neurotoxicity (U.S. EPA, 1998a, b) and delayed developmental effects that may occur later in life as a result of prenatal or postnatal exposure to any type of

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pesticide (U.S. EPA, 1999). This effort is of the enhanced emphasis on children's health mandated by the Food Quality Protection Act of 1996.

OPP has developed a specific test guideline for screening OP compounds for acute and delayed neurotoxicity (U.S. EPA, 1998b). This test guideline was developed specifically to identify those OP compounds that cause OP-induced delayed neurotoxicity (OPIDN), a syndrome characterized clinically by limb weakness and upper neuron spasticity, pathologically by distal axonopathy of peripheral nerve and spinal cord, and biochemically by inhibition and "aging" (i.e., the covalent binding with the OP) of neurotoxic esterase in neural tissues. The inhibition and aging of the neurotoxic esterase enzyme is highly correlated with the initiation of OPIDN, and this test guideline calls for biochemical measurements of neurotoxic esterase. The applicability of the test guideline to inorganic metallic, organic, or organometallic substances other than OP compounds has not been investigated. In theory, it would seem that it could be applicable in the identification of any compound that causes delayed neuropathy, provided that the mechanism by which the compound causes delayed neuropathy is the same as that of OPs.

Although the Agency does not actively or formally look for evidence that chemicals cause delayed toxic effects (other than cancer), when data or other evidence are identified that indicate that this may occur, it is considered as part of the overall assessment. Depending on its nature and severity, the Agency may chose the delayed effect over other toxic effects to derive an endpoint to be used for risk assessment or other purposes. For example, the inhalation reference concentration (RfC) of 0.02 $\mu g/m^3$ established for beryllium and beryllium compounds is based in part on the observation of delayed toxicity (i.e., the occurrence of chronic beryllium disease discussed above) (USEPA IRIS database). Because metals do not degrade in biological tissue and can persist for long periods of time in human subjects, it would seem plausible that metals may have a greater propensity to cause delayed effects as compared with organic chemicals. It may be prudent, therefore, for a human health assessment of a metal to attract more interest than what is currently given to the possibility that the metal causes delayed effects.

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3.3.5.2. Limitations

As noted above, EPA, as a general practice, does not actively or formally look for evidence that the chemical may cause delayed toxic effects, other than cancer. This may stem from the inherent difficulties in identifying and characterizing a causal relationship between an observed toxic effect and exposure to a particular chemical that took place months, years, even decades prior to the onset of toxicity. Such a characterization is confounded by many obvious factors, the most fundamental of which is determining whether the observed effect is even chemical induced and, if so, delineating the culprit chemical from the myriad other chemicals to which there was exposure. In addition, testing for delayed effects in experimental animals to predict similar effects in humans can be difficult, particularly in maintaining the needed resources to monitor previously exposed animals over a prolonged period. Furthermore, the latent period in animals may differ from that in humans, a well-recognized area of scaling where "physiological time" becomes an important concept. For example, development of mesotheliomas after exposure to asbestos takes approximately 30 years to manifest in humans, whereas only a 10-year latent period is required in dogs.

To date, many of the generally accepted characterizations of a causal relationship between exposure to a chemical and a delayed effect are made from anecdotal or epidemiological observations. More precisely, these characterizations are often made only when the delayed effect is observed in many people who were previously engaged in similar activities that led to the exposure and when the culprit chemical can still be found in the human subjects. The determination that inhalation of poorly soluble beryllium can cause chronic beryllium disease up to years later and that exposure to lead early in life may contribute to health problems later in life are classic examples.

3.3.6. SENSITIVE SUBGROUPS AND LIFE STAGES/SUSCEPTIBILITY FACTORS

There are subgroups of populations and life stages that are uniquely sensitive to adverse effects resulting from exposure to metals or other chemicals. These sensitive subpopulations will show a different or enhanced response when compared with that of the general population. They

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include groups in various life stages (fetus, child, adult, elderly) and of different genders, those having genetic polymorphisms (e.g., Wilson's disease, which results in excessive copper retention) or pre-existing diseases (e.g., asthma), and those that differ in nutritional status and lifestyle choices (smoking, consuming alcohol). These and other susceptibility factors are discussed in detail in Goyer et al. (2003).

The one potentially susceptible subpopulation that the Agency has increased its awareness of in the toxicological assessment of chemical exposure is children (including the fetal stage). Compared with adults, children are potentially at greater risk of exposure to chemicals. In proportion to their size, children may breathe more air, drink more water, and eat more food than do adults, thereby receiving a higher dose (mg/kg-body weight). There are also differences in pharmacokinetic behavior of metals at difference stages in the life cycle, particularly for the nutritionally essential metals (WHO, 1996). During the immediate postnatal period, absorption of essential metals (e.g., chromium, iron, zinc) is poorly regulated until homeostatic regulatory mechanisms become established with increasing gut maturity, and metal absorption declines again in the elderly. (Additional information on developmental toxicological variability in children can be found in Graeter and Mortenson, 1996). Furthermore, children, especially toddlers, are exposed through different routes than are adults, such as hand-to-mouth activity resulting in incidental ingestion of soil, toys, or other objects (U.S. EPA, 2002).

3.3.6.1. Application

The question is whether additional safety or uncertainty factors need to be considered for the assessment of exposure to a metal for potentially sensitive subpopulations. An example of when these types of factors have been used with organic substances is the inclusion of 3X to 10X uncertainty factors for children's risks from organophosphates in addition to the conventional 10X factors for interspecies extrapolation and intraspecies variability (U.S. EPA, 1998). These factors were added in cases when the lowest-observed-adverse-effect level (LOAEL) was used to establish a safety recommendation because a no-observed-adverse-effect level (NOAEL) was not determined in the critical study or a single sex human study was the only study used or available for the assessment. However, Burin and Saunders (1999) suggest that the intraspecies

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uncertainty factor, in the range of 1 to 10, is protective of 99% or more of the human population, so additional safety factors for potentially sensitive subpopulations are not needed. In fact, U.S. EPA (2002) "A Review of the Reference Dose and Reference Concentration Processes" concluded that the existing uncertainty factors and the process by which RfD/RfCs are derived are adequate to address any potential differences in susceptibility of children vs adults.

For certain metals, sensitive subpopulations are known (e.g., genetic predisposition to copper poisoning, childhood sensitivity to developmental effects of lead). For these metals, NOAELs can be developed for these particular populations; therefore, additional safety factors are not needed. For other metals, additional safety factors may be included in the assessment if sensitive subpopulations (e.g., children, the elderly) are of particular concern, although this is not recommended for routine assessments.

3.3.6.2. Limitations

There is minimal information on the types of potentially susceptible subpopulations that may exist with regard to exposure to metals. The only way to determine whether a susceptible subpopulation exists is to examine the dose-response effects in the various segments (life stage, gender, health, nutritional status, etc.) of the total exposed population. More information about the metal, including its toxicokinetics, similarity of effects in more than one animal species or humans, mode of action, and temporal relationship (time between exposure and effect) (U.S. EPA, 2002) will aid in this analysis of whether safety factors should be added in the assessment.

3.3.7. BACKGROUND

Metals are natural components of the environment and are detected at various levels in air, soil, water, and food. The contribution of the background level of a metal(s) to the cumulative exposure of people may be significant and so should be considered in any exposure and safety

> The ***background concentration*** of metals is mostly due to input from natural sources, such as weathering of rocks, soil formation, and siltation. Additional material has been deposited into the environment over the centuries by humans, elevating the natural background levels to what is known as ***ambient concentrations*.**

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assessment (see Section 3.2. Exposure - background). Lifestyle choices expose people to metals in many different contexts that need to be considered when assessing the added risk caused by a particular source. For example, cadmium is one of the many chemical components of tobacco, and it can significantly affect a person's total exposure, thereby reducing the amount that should be consumed in foods.

However, the added risk from dietary or other point sources must be considered in light of RBA of the background and additional sources. Background metals generally are reduced in bioavailability due to aging in soils or sediments (see Section 3.1.7.) or transformation to less bioavailable salts.

3.3.7.1. Application

All relevant routes of natural background exposure need to be included in the assessment to determine total exposure (background + point source). These routes are primarily oral (which includes hand-to-mouth transfer, as well as the dietary route) and inhalation. However, exposures from each route must be normalized for bioavailability so that only the bioavailable fractions of each source are added for total exposure.

3.3.7.2. Limitations

There are several limiting factors in assessing the contribution of the background exposure of a metal to the overall exposure for human health effects assessments. First, the speciation of the metal must be the same for both the estimate of background exposure and the estimate for the added exposure that is of concern. For example, organic arsenic in the form of arsenobetaine is a natural component of shellfish, so an estimate of total arsenic exposure would suggest that those who eat a diet high in shellfish would be at significant risk from environmental arsenic exposures. However, the organoarsenicals are not very toxic, and thus actually contribute very little to the overall risk from the inorganic arsenic generally found as an environmental pollutant. Better analytical methods are needed to differentiate between these two forms of arsenic, particularly at the low concentrations found in human urine.

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Cationic metals differ in their bioavailability, so inclusion of the naturally occurring concentrations of metals in the sulfide forms or as insoluble salts to the total exposure analysis may greatly overestimate actual target dose. Determining the bioavailability of a metal from different exposure scenarios (air, diet) is also important, because absorption may not be equivalent across the different routes. Good analytical tools are required to determine the complete spectrum of metals present and their relative bioavailabilities in the environment of interest.

3.3.8. PHARMACOKINETIC DATA AND PBPK MODELS

Pharmacokinetic data can be used to decrease uncertainty in the risk assessment process. Methods to incorporate consideration of pharmacokinetic data include (from most to least data intensive) (1) simple default adjustments (e.g., application of default uncertainty factors), (2) use of categorical default adjustments (e.g., dosimetric adjustments applying to a range of metals or metal species on the basis of similarities in solubility, bioavailability, toxicity, etc.), and (3) use of a chemical-specific PBPK model. Evaluation of the extant pharmacokinetic database for any metal should explicitly consider the issues outlined in Table 15. Although some of these factors (e.g., bioavailability) are not traditionally considered pharmacokinetics, they can directly modify oral or GI uptake and hence impact estimation of absorbed dose.

> ***PBPK models*** make it possible to evaluate the relationship of different dose metrics to the toxic effect of concern and guide the selection of an appropriate dose metric. A ***dose metric*** is a measure of the amount or concentration the active form of metal to the target organ or tissue over an appropriate time period.

3.3.8.1. Application

In considering the use of a published PBPK model for risk assessment, the model itself needs to be assessed. This involves a determination that the model representation (conceptual, functional, computational) and parameterization (blood flows, organ volumes, biochemical and metabolic parameters) are adequately documented and appropriate for the intended use. Whether

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the model is adequately predictive of independent data sets (i.e., data not used in model development) also must be given consideration. Guidelines exist for model evaluation, and these should be used as a framework to determine whether a particular model is appropriate for use in risk assessment (Andersen et al., 1995; Clark et al., 2003).

3.3.8.2. Limitations

The high data requirements for PBPK models can limit the utilization of the results. The lack of specific data will increase the uncertainty in risk assessments. Data gaps or default assumptions for PBPK model key criteria will also reduce applicability. Constructive application of a PBPK model requires that several key criteria be met that can be determined by evaluation of the health effects data for the metal. These criteria are (1) identifying toxic or active form(s) of the metal, (2) selecting the appropriate dose metric, and (3) identifying appropriate target organ or cells on the basis of the health effect of greatest concern.

Identifying the toxic or active form of metals is, on one level, simpler when compared with identifying that of many organic chemicals because metals (excluding metalloids, e.g., arsenic) tend to be minimally metabolized. However, the complication is that differing valence states (i.e., species) can have differing toxicity (O'Flaherty, 1998). In addition, the ability to evaluate this issue may be compromised, depending on study design and the availability of analytical technology to speciate the metal. In the absence of information concerning the toxic form of the metal, it is generally assumed that the entire amount reaching the target tissue/organ is in the toxic form. If incorrect, this will have the effect of overestimating dose to target tissue and, hence, risk.

Selection of the health effect of greatest concern for a particular metal and identification of the target organ/tissue will depend on evaluation of the health effects database in its entirety. A critical consideration will be to match the toxic endpoint with the active form of the metal in cases where there are sufficient data to suggest that there are one or more active forms of the metal or metalloid (e.g., arsenic). For some acute health effects, measures such as peak concentration are more closely related to the probability of developing an adverse response (e.g., irritation). For many chronic effects, the cumulative amount of active chemical delivered to the organ (e.g, AUC) or time above a critical concentration may be better correlated with the probability of developing a toxic response.

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Table 15. Kinetic Factors to Consider When Evaluating the use of PBPK Models or Other Dosimetric Adjustments in the Metals Risk Assessment Process

Kinetic factor	Determinants to Evaluate
Inhalation bioavailability	Particle size Solubility of metal species
Oral bioavailability	Soil or dust matrix Particle size Solubility of metal species in GI tract fluids pH of stomach contents Amount of stomach contents (including fed vs. fasted) Host factor influence (age, nutritional status) Dietary interactions (food matrix)
Cellular uptake[a]	Carrier-mediated uptake (e.g., phosphate or sulfate transporters) Facilitated transport in the form of organic complexes
Toxic metal-essential metal interactions[b]	Competition for binding sites on membrane transport proteins Interactions at enzyme active sites Systemic level interactions altering absorption
Protein binding	Capacity limited binding to specific proteins Inducibility of binding proteins (e.g., metallothionine) Protein binding as sequestration mechanism vs. mechanism of action
Sequestration in bone	Mechanisms (e.g., effects of bone formation and resorption, migration within the bone matrix) Age dependence (e.g., effects of growth) Effect on overall physiologic residence time
Metabolism	Differential toxicity of metal species or methylated metabolites Relative contribution to overall elimination compared to excretory mechanisms
Excretion	Relative contribution of urinary and biliary elimination Capacity limitation (saturation kinetics)

[a] Note review by Dawson and Ballatori, (1995).
[b] See reviews by Goyer (1997) and Peraza et al. (1998).

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3.3.9. TOXICITY TESTING

> For ***noncancer health effects***, anticipated doses are compared with thresholds or reference doses (RfDs) with determine whether adverse effects are likely. Cancer risks are described as incremental increases in the probability of contracting ***cancer***, as assessed on a population basis.

Toxicity values for metals occur within the same databases as those for other compounds. The primary database for human health toxicity values is the Integrated Risk Information System (IRIS) maintained by EPA (http://www.epa.gov/iriswebp/iris/index.html). The IRIS program provides 42 metal-associated RfDs, including independent RfDs for seven different thallium salts and a single RfD for "beryllium and compounds." Some RfDs identify a general subcategory of the metal (inorganic, soluble, elemental). This issue is not unique to metals; a similar variability is found in the designation of RfDs for organics. For example, the RfD for xylenes includes all three structural isomers, di-methyl-substituted xylenes, and mixtures, and there is an oral RfD for trans-1,2 dichloroethylene that excludes the cis-isomer.

3.3.9.1. Application

To achieve an adequate internal dose for the study of toxicity, animal toxicologists often use bioavailable form of metals. For the initial characterization of a toxicity syndrome, it is not practical to simultaneously test all forms of a metal that may be involved in human exposures. For example, aluminum researchers commonly use aluminum lactate, which is known to reliably provide elevated tissue concentrations in laboratory animals. Aluminum maltolate is also used because it provides a stable ion pool in water solution, as opposed to other salts that are progressively hydrated as the solution stands. However, a site assessor is very unlikely to encounter aluminum in the lactate or maltolate form. Thus the situation arises where toxicity data have been generated for a bioavailable form of a metal, but the site assessor must deal with another form.

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Several approaches are possible:

1. Use a default assumption that the metal in the environmental samples is in its most toxic form. This is the most health-conservative approach.

2. Use adjunct scientific data to derive an adjustment to the effective dose identified in the animal study. An example of adjunct data useful for generalization from the administered to the encountered form can be provided for aluminum. Pharmacokinetic information for several aluminum forms has been provided in review articles (Yokel and McNamara, 2001; DeVoto and Yokel 1994). Other studies provide data on tissue concentration after dosing with equivalent molar amounts of different aluminum salts (Dlugaszek et al., 2000). An empirical comparison of the LD50 of a number of administered salts is also available (Llobet et al., 1987), and another series of studies looked at developmental toxicity of several salts (Domingo, 1995).

3. Conduct new animal toxicology studies using the metal form encountered in the assessment. Coordination with the National Institute of Environmental Health Services' National Toxicology Program will be necessary.

4. Estimate bioavailability through solubility studies or limited bioavailability studies of samples and/or the continued development of models addressing forms of metals in the environment and their toxicity. For example, arsenic bioavailability has been estimated for soils from various contaminated sites (Freeman et al., 1995, 1993; Ng et al., 1998) and also through a series of solubility studies of soil from a site contaminated with mine tailings (Ng et al., 1998; Salocks et al., 1996).

3.3.9.2. Limitations

The scientific literature amply demonstrates that the pattern, effective doses, and species-specific toxicity of a metal will vary widely depending on its form. A major challenge is that emissions and exposure data for metals are typically reported as a total elemental metal or, occasionally, as metal categories (e.g., sulfides of nickel or nickel compounds) but not as a specific species (e.g., nickel subsulfide). Risk assessors are often faced with making simplified assumptions when comparing exposure with toxicity data that are not concordant for the species or route of exposure. For example, the inhalation toxicity data for nickel subsulfide are quite

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good, but the data for nickel oxide (the most commonly inhaled form of nickel) are limited. The selection of these assumptions and defaults should be based on good scientific judgement, and the exposure and toxicity data should be as consistent as possible. New toxicity studies need to be coordinated with parallel efforts to develop methods to sample and speciate priority metal compounds to resolve exposure with toxicity assessments.

Resolution of these issues may require adjusting toxicity testing methods to address metal species, continued development of validated in vitro methods to estimate bioavailability, use of adjustment factors to relate toxicity data to environmental media, and the application of models addressing forms of metals in the environment and their toxicity.

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3.4. CHARACTERIZATION OF ECOLOGICAL EFFECTS

Metals are naturally occurring substances and, as such, organisms have evolved mechanisms for maintaining homeostasis in the presence of expected exposure levels. However, areas of metals enrichment, particularly when generated by anthropogenic activities, can pose challenges to organisms. Toxicity assessment for ecological receptors exposed to metals requires an understanding of both the natural mechanisms for tolerance for (or, in the case of micronutrients, the use of) metals and the toxicological responses that occur when exposure exceeds the capacity of the organism to regulate its body burdens. Furthermore, risk assessments for metals are further complicated by the need to express the dose-response (or concentration-response) functions of bioavailable units that are functionally equivalent to measures of exposure. This section provides tools and approaches for addressing issues of essentiality, appropriate toxicity tests, novel endpoints (e.g., gene expression), and acclimation or adaptation to continued exposures.

3.4.1. ESSENTIALITY

> ***Essentiality***, or the requirement for normal organism metabolic function, of many metals is one of the primary factors that differentiates risk assessment for metals and metal compounds from that of synthetic organic chemicals.

Essentiality, or the requirement for normal organism metabolic function, of many metals is one of the primary factors that differentiates risk assessment for metals and metal compounds from that of synthetic organic chemicals (Janssen and Muyssen, 2001). Trace elements, such as cobalt, copper, iron, manganese, selenium, molybdenum, and zinc, are necessary for the normal development of

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plants and animals. In many cases, these metals are added to animal feed and pharmaceutical products (SRWG, 2002) or to plant fertilizers. Other metals, such as arsenic, cadmium, lead, and mercury, have no known beneficial uses. Trace elements can be divided into three groups:

1. Those known to be essential.

2. Those that have beneficial metabolic effects but have not been shown to be essential.

3. Those that occur widely in living organisms but seem to be only incidental contaminants and are not known to be beneficial (Mertz, 1981).

Table 16 classifies the metals addressed in this framework by their known essentiality to organisms. The concept that many metals are required for organism health at one range of concentrations and are toxic in quantities outside of that range has been referred to as the "window of essentiality" (Hopkin, 1989) or the "optimal concentration range" for essential elements (Alloway, 1995; Fairbrother and Kapustka, 1997; Van Assche et al., 1997). For essential elements that exhibit biphasic dose-response curves (Figure 8, above), adverse effects resulting from deficiency should be considered, as well as those that result from excessive exposure. Recognition of the window of essentiality, as well as consideration of the biochemical and physiological processes that regulate metals within living organisms, are both important components of ecological effects assessment (Abernathy et al., 1993).

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Table 16. Metals classified by their known essentiality

Metal	Essential (known requirement for health and function)		Beneficial (but not known to be essential)		Nonessential (and not known to be beneficial)
	Plants	Animals	Plants	Animals	
Aluminum (Al)					x
Antimony (Sb)					x
Arsenic (As)					x
Barium (Ba)					x
Beryllium (Be)					x
Cadmium (Cd)					x
Chromium (Cr)		x			
Cobalt (Co)		x	x		
Copper (Cu)	x	x			
Lead (Pb)					x
Manganese	x	x			
Mercury (Hg)					x
Molybdenum	x	x			
Nickel (Ni)	x	x			
Selenium (Se)		x	x		
Silver (Ag)					x
Strontium (Sr)					x
Thallium (Tl)					x
Vanadium (V)				x	
Zinc (Zn)	x	x			

Source: Adapted from a table presented in SRWG (2002) and incorporating data from NRC (1980) and Barak (1999). Fairbrother and Kapustka (1997) discussed the roots of essentiality of naturally occurring elements.

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3.4.1.1. Application

The optimal concentration range (or safe intake range) for essential elements must ensure that effects thresholds such as toxicity reference values (TRVs) are not lower than the nutritional requirements for the particular plant or animal species being evaluated. Where TRVs or other effects concentrations (or doses) are intended as thresholds for detrimental effects due to excessive intake), care must be taken to ensure that these toxicity thresholds for essential metals are at the upper end of the optimum range or sufficiency range (at the point where toxic effects begin to occur). If set too low (i.e., in the range where deficiency can occur), the determination of risk will be erroneous. For wildlife, the literature on dietary requirements of essential elements for livestock can be consulted. The NCR has published useful summaries (NRC, 1980, 1994), and McDowell (2003) updates this information. Minimum concentrations required for plant growth are summarized in Epstein (1965, 1972).

> For essential elements, it is important to ensure that effects thresholds, such as toxicity reference values (TRVs), are not lower than the nutritional requirements for the plant or animal species being evaluated. It may be difficult, however, to directly compare toxicity threshold values with recommended dietary requirements because of differences in test conditions among published studies.
>
> In screening level assessments, toxicity threshold values are advised for application, if they are no more than 10-fold lower than estimated requirements. Otherwise, the required levels can be used as a threshold for allowable exposures. Higher-tiered assessments may require additional bioassays to characterize the biphasic dose-response curve and determination of both required and excessive threshold levels.

3.4.1.2. Limitations

Because of differences in test conditions among published studies, it may be difficult to directly compare toxicity threshold values with recommended dietary requirements of essential elements. Extrapolation of data among species (e.g., from livestock to wildlife species) may also add uncertainty to the effects assessment. Further, addition of safety factors when deriving protective values often results in concentrations significantly below required intake.

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Derived toxicity threshold values should be used in screening-level risk assessments if they are no more than 10-fold lower than estimated requirements. Otherwise, the required levels should be used as a threshold for allowable exposures. Higher-tiered assessments, where more accurate estimates of effects thresholds are expected, may require additional bioassays to characterize the biphasic dose-response curve and determination of both required and excessive threshold levels. See the following sections for considerations of bioavailability factors, mixtures of multiple metals, and interspecific extrapolations.

3.4.2. ACCLIMATION AND ADAPTATION

Organisms have developed various mechanisms to cope with variable background metal concentrations, particularly for those metals that are essential elements (Table 23). If the amount is less than required, passive or active uptake mechanisms are used to enhance internal concentrations, whereas during periods of excessive amounts exclusion mechanisms come into play. These various approaches to homeostasis are discussed in detail in Kapustka et al. (2003). Additionally, organisms can acclimate to suboptimal metal levels by changing various physiological functions, or populations can undergo genetic adaptation and develop increased tolerance to different levels (Wallace and Srb, 1961).

The genetic makeup of an organism defines its ability to cope with environmental conditions. Genes can be expressed or remain "silent," and shifts in gene expression can occur when the environment changes. Furthermore, organisms use different portions of their total array of genetic information in different life stages. This shifting of tolerance within the genetically defined limit of the organism is known as *acclimation*.

> ***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 life times. Adaptation is also known as ***genotypic plasticity***.

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Physiological changes induced by acclimation may be reversed if the environment reverts to the original conditions. Tolerance acquired through physiological acclimation processes is not always passed on to offspring; however, the same genetic information that allowed acclimation to occur in the parents will be passed on, so the offspring will retain the ability to acclimate in a similar fashion. If the offspring develop in the altered environment, they will express the set of genes most appropriate for tolerance of those conditions.

Genetic *adaptation* results from increased survival of tolerant genotypes and subsequent changes in gene frequencies. However, linking these genetic changes to increased tolerance in the field and identifying the specific mechanisms responsible has proven challenging. Laboratory experiments conducted with F_1 generations obtained from metal-contaminated habitats provide the strongest evidence to support a genetic basis of tolerance (Klerks and Levinton, 1993), and new methods in toxicogenomics (e.g., microarrays) are providing additional insights.

Evidence of adaptation (convergent evolution) for metal tolerance in plants comes from the fact that plants of diverse taxonomic relationships grow on soils high in metals. Metal-tolerant flora have been described for soils high in zinc, nickel, chromium, and copper (Antonovics et al., 1971; Brooks, 1972). These reviews indicate that some species are restricted to the high-metal soils, but other species exist across a broad concentration range. These represent differences in niche breadth (i.e., those restricted to high-metal soils vs. those occurring in soils that have either high or low concentrations of metals).

> Considerable evidence supports the hypothesis that previously exposed populations will be tolerant to metals, both physiological acclimation and adaptation to contaminants may have specific costs. For example, induction of metal-binding proteins increases metals tolerance, but also uses energy normally available for other metabolic processes (e.g., growth, reproduction). Similarly, genetic changes associated with metals exposure might harm populations. Reduced genetic diversity has been reported in populations exposed to contaminants and may result in population bottlenecks, as well as increased susceptibility to other stressors.

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Metal adaptation in plants often is accompanied by metal adaptation in co-located animals, as selection for metal tolerance is expected to improve fitness in exposed conditions (Posthuma and Van Straalen, 1993). Compared with other environmental parameters, metal exposure is regarded as a strong and stable selective force, and it leads to rapid evolution of tolerance (Posthuma and Janssen, 1995). Metal-tolerant animals tend to grow fast, mature early, and have a high excretion efficiency (Posthuma and Janssen, 1995).

Metal adaptation in natural populations of terrestrial invertebrates also has been demonstrated conclusively for several animals: the terrestrial isopod *Porcellio scaber* and the springtails *Orchesella cincta, Isotoma notabilis*, and *Onychiurus armatus* (Posthuma and Van Straalen, 1993). Metal tolerance also has been demonstrated in ticks and a fly species in response to the application of a metal-based pesticide. There is evidence for increased metal tolerance in other species, but acclimation and adaptation could not be distinguished (Posthuma and Van Straalen, 1993).

Although there is considerable evidence to support the hypothesis that previously exposed populations will be tolerant to metals, both physiological acclimation and adaptation to contaminants may have specific costs. For example, although induction of metal-binding proteins increases tolerance to subsequent metal exposure, it also uses energy normally available for other metabolic processes (e.g., growth, reproduction). Similarly, genetic changes associated with exposure to contaminants might harm populations. Reduced genetic diversity has been reported in populations exposed to contaminants and may result in population bottlenecks. Furthermore, as tolerant genotypes are eliminated from a population, the reduced genetic diversity may increase the susceptibility of this population to other stressors.

3.4.2.1. Application

A summary of metal tolerances by plants and livestock is presented in Table 17. It should be noted that the NRC (1980) committee that identified the maximum levels of metals tolerated by domestic livestock based its conclusions on data from toxicological-type feeding studies in which soluble metal salts had been mixed with practical or purified diets to examine animal

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response to the dietary metals. If soil is incorporated into diets, metal solubility and bioavailability may be much more limited than in the tests relied on by the NRC. For example, it has been noted that until soil exceeds about 300 mg Pb kg^{-1}, animals show no increased body burden from ingesting the soil (Chaney and Ryan, 1993). Other metals in equilibrium with poorly soluble minerals or strongly adsorbed in soils are often much less bioavailable than they would be if they occurred in more soluble salts.

It has been shown in studies with *Daphnia* and algae that acclimation of test organisms to culture conditions will significantly influence the outcome of toxicity tests (Janssen, 19??). Presumably, similar effects occur with terrestrial organisms (e.g., earthworms or springtails) (see Fairbrother et al., 2002). Thus, organisms should be acclimated to the same waters or soils that will be used in the toxicity studies for several weeks prior to study initiation. This will avoid shocking the organisms by placing them in test conditions that have significantly depleted or elevated levels of endogenous metals (e.g., those that are not the subject of the toxicity study) and ensure that any adverse effects are actually due to the metal in question. However, it is not possible to conduct pre-acclimation for soil microbial studies because in situ populations of microorganisms from previously collected soils are used. This calls into question the applicability of results from microbial function studies, and until these issues are resolved, results should not be used for setting soil criteria (U.S. EPA, 2003 - EcoSSLs).

Most research examining tolerance to metals has focused on population-level responses, although consequences at the community level also occur. The most

For site specific assessments, the concept of **pollution-induced community tolerance (PICT)** has been proposed as a tool to assess community level effects. PICT is tested by comparing responses of communities collected from polluted and reference sites to contaminant exposures under controlled conditions. The increase in community tolerance at a polluted site that results from the elimination of sensitive species is considered evidence that this restructuring was caused by the pollutant.

Extrapolation of these results to communities of terrestrial plants and animals must be done with caution, since most of the original research on PICT has been conducted using small organisms with relatively fast life cycles (e.g., benthic invertebrates, soil microbial communities).

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common explanations for increased tolerance of populations within communities include acclimation and selection for resistant genotypes. However, because communities consist of large numbers of interacting species, it is likely that other mechanisms unique to these systems will contribute to increased tolerance. For example, the replacement of sensitive species by tolerant species, termed "interspecific selection" (Blanck et al., 1988), is a common response in polluted systems and one of the most consistent indicators of metal pollution. Pollution-induced community tolerance (PICT) has been proposed as an ecotoxicological tool to assess effects of contaminants on communities (Blanck et al., 1988). PICT is tested by comparing responses of communities collected from polluted and reference sites to contaminant exposures under controlled conditions. The increase in community tolerance at a polluted site that results from the elimination of sensitive species is considered evidence that this restructuring was caused by the pollutant.

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Table 17. Maximum tolerable levels of dietary minerals for domestic livestock in comparison with levels in forages

Element	Soil-plant barrier	Level in plant foliage[a]		Maximum levels chronically tolerated[b]			
		Normal	Phytotoxic	Cattle	Sheep	Swine	Chicken
		mg/kg^{-1} dry foliage		mg/kg^{-1} dry diet			
As (inorg.)	Yes	0.0l–l	3–l0	50	50	50	50
B	Yes	7–75	75	150	~150	~150	~150
Cd[c]	Fails	0.1–1	5–700	0.5	0.5	0.5	0.5
Cr^{3+}	Yes	0.1–1	20	~3000	~3000	~3000	3000
Co	Fail?	0.01–0.3	25–100	10	10	10	10
Cu	Yes	3–20	25–40	100	25	250	300
F	Yes?	1–5	–	40	60	150	200
Fe	Yes	30–300	–	1000	500	3000	1000
Mn	?	15–150	400–2000	1000	1000	400	2000
Mo	Fails	0.1–3	100	10	10	20	100
Ni	Yes	0.1–5	50–100	50	~50	~100	~300
Pb[c]	Yes	2–5	–	30	30	30	30
Se	Fails	0.1–2	100	~2	~2	2	2
V	Yes?	0.1–1	10	50	50	~10	10
Zn	Yes	15–150	500–1500	500	300	1000	1000

[a]Based on literature summarized in Chaney et al., 1983.
[b]Based on NRC, 1980. Continuous long-term feeding of minerals at the maximum tolerable levels may cause adverse effects. NRC estimated the levels in parentheses by extrapolating between animal species when data were not available for an animal.
[c]NRC based the maximum levels tolerated of Cd or Pb in liver, kidney, and bone in foods for humans rather than simple tolerance by the animals. Because of the simultaneous presence of Zn, Cd in animal tissues is less bioavailable than Cd salts added to diets.

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Naturally occurring levels of metals play an important role in biogeographic distributions of plants and animals and may, in fact, be limiting factors in species distributions or use of landscapes. Therefore, it is difficult to make generalizations about effects levels that are applicable and consistent to all organisms in all habitats, and it becomes very important to clearly define the geospatial location of the area to which the assessment results will apply. For site-specific assessments, the assessment results will be directly applicable to the entire range of species that may be found on that site (although for assessments conducted over large areas of >50 sq miles, it is possible that multiple soil types and other local landforms may result in significant differences in metal bioavailability and plant communities).

For 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 must be taken, however, that the organism-environment combinations that are assessed are, in fact, compatible with real-world conditions. For example, benthic organisms generally associated with slow-moving, warm waters would not be expected to tolerate conditions of high metal biovailability such as occurs in faster-moving, colder waters that have little organic matter. Thus, for site-specific assessments, species tested and water (or sediment) used in the test system should be similar to conditions at the site. In the absence of such information, data from standard test species and conditions could be used, but uncertainty factors may be needed be adjust the final toxicity value accordingly.

More appropriately, single-result assessments for the entire country should be avoided. Rather, such assessments should be subdivided into metal-related ecoregions (known as "metalloregions," McLaughlin and Smolders 2001) so 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 WQC (Griffith et al. 1999). The value of metalloregions is that they provide the conceptual framework to account not only for the broad regional parameters affecting metal availability in soils and waters, but also for the differences in organism response to added metal.

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3.4.2.2. Limitations

> For national scale assessments the entire country can be subdivided into metal-related ecoregions (known as "metalloregions"), to help ensure that protection levels, mitigation goals, and ranking results will be appropriate for the suite of species naturally present within each type of controlling environment. However, the metalloregion concept has not yet been applied to all the US.

Although there is considerable evidence to support the hypothesis that previously exposed populations will be tolerant to metals, both physiological acclimation and adaptation to contaminants may have specific costs (Wilson, 1988). For example, although induction of metal-binding proteins increases tolerance to subsequent metal exposure, it also uses energy normally available for other metabolic processes (e.g., growth, reproduction). Similarly, genetic changes associated with exposure to contaminants might harm populations. Reduced genetic diversity has been reported in populations exposed to contaminants and may result in population bottlenecks. Furthermore, as tolerant genotypes are eliminated from a population, the reduced genetic diversity may increase the susceptibility of this population to other stressors. There is theoretical support for the hypothesis that populations adapted to contaminants have higher metabolic costs or are more susceptible to other stressors; however, few empirical studies have demonstrated increased costs.

One of the assumption behind the use of PICT as an ecotoxicological tool is that differences in tolerance among communities can be detected using short-term experiments. This significantly constrains the application of PICT as an assessment tool. Although tolerance at the population level can be assessed using a variety of species, logistical considerations will limit the types of communities where tolerance can be investigated experimentally. Most of the original research on PICT has been conducted using small organisms with relatively fast life cycles (e.g., benthic invertebrates, soil microbial communities). Therefore, extrapolation of these results to communities of terrestrial plants and animals must be done with caution.

The metalloregion concept (McLaughlin and Smolders, 2001), although intuitively appropriate, has not yet been fully developed for the United States. The country has been divided into ecoregions for both aquatic and terrestrial systems (Bailey et al., 1994, Bailey, 1983). These

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are based on climactic and vegetation factors and form the basis of metalloregions. EPA is still working to complete ecoregion maps at much finer scales for each state (See EPA website: http://www.epa.gov/wed/pages/ecoregions/ecoregions.htm). To complete the metalloregion concept, soil properties that affect bioavailability (e.g., pH, CEC, and OM) need to be overlayed on the ecoregions, along with soil type (e.g., sandy loam, clay loam, etc.) and background metal concentratons of metals. Similar information is needed for water bodies. Although this type of information is fairly current and available, soil data have not been updated since the mid-1970s, which may limit their usefulness to some extent. Nevertheless, work is underway to develop metalloregions, although it is likely to be several years from the time of this writing before they are available for use in a decisionmaking capacity.

3.4.3. METALS MIXTURES

Mixtures of metals (including metalloids, as well as other contaminants) are commonly encountered in the natural environment as a result of anthropogenic inputs. Metal interactions, according to Calamari and Alabaster (1980), occur at three levels:

1. Chemical interactions with other constituents in the media;
2. Interactions with the physiological processes of the organism during uptake; and
3. Interactions at the site of toxic action.

Much of the difficulty in interpreting the available information on the toxic effects of metal mixtures is due to differing measures and definitions of the bioavailable fraction of metals, whether it is the fraction that is available for uptake from the environment or at the site of toxic action. Some measure of the bioavailable metal fraction in the exposure media is needed to accurately predict the effects of metals and metal mixtures (Ankley et al., 1996; Posthuma et al., 1997; Sauvé et al., 1998; Weltje, 1998; Di Toro et al., 2001). Characterization of effects of metal

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mixtures has also been reported to be concentration dependent (Spehar and Fiandt, 1986; Herkovits et al., 1999; Fargašová, 2001; Mowat and Bundy, 2002).

3.4.3.1. Application

Two key questions need to be addressed by effects assessments related to metal mixtures: (1) To what extent does each metal contribute to any observed effect? (2) Are the effects significantly greater or lesser than the sum of the individual component effects? The answers to these questions also have the potential to affect water quality guidelines (WQGs), EcoSSL values, clean-up targets, and other similar management decisions.

Methodologies (graphical and statistical) to predict impacts of metal mixtures and interactions of individual metals within mixtures can be broadly classified as either concentration addition models or effects addition models. Both models use metal water concentrations to generate concentration-response curves for individual metals, and these data are then used to generate specific critical concentrations for mixture models. Similar models can be developed for soils or sediments.

In the concentration addition model, all metals in a mixture are added together to predict toxicity, with differing potencies taken into account by converting chemical concentrations to an equitoxic dose (e.g., toxic units (TUs) or toxicity equivalence factors (TEFs), which convert all metals to one metal concentration). In the effects addition model, differing potencies are ignored, and the effect of each metal's concentration in a mixture is combined to predict mixture toxicity. Both models allow detection of toxicity greater than predicted (more than additive), the same as predicted (strictly additive), or less than predicted (less than additive).

The TU approach involves deriving dimensionless units for each metal in a mixture by dividing individual concentrations by their individual toxic concentrations (such as LC_{50} values). The TUs for all the metals in the test mixture are then summed. A value of 1 ± 0.1 in the case of an LC_{50} would predict 50% mortality (or another effect if TUs are based on that effect rather than on lethality). A value significantly greater than 1 would predict more than 50% mortality. A value significantly less than 1 would predict less than 50% mortality.

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The TU approach can be used with any endpoints, for instance LC_{50} or EC_{50} values. The toxic concentration can be derived from guideline values (e.g., WQGs), from literature toxicity data, or from specific experiments. This approach can be used when setting WQC. It has, for example, been recommended for use as part of the Australia and New Zealand WQGs (ANZECC and ARMCANZ, 2000). These guidelines employ a concentration addition approach using WQG concentrations of metals as TUs:

$$TTM = \sum(C_i/WQG_i)$$

where TTM is the predicted total toxicity of the mixture, C_i is the concentration of the component, and WQG_i is the guideline for that component. If TTM exceeds 1, then the mixture has exceeded the water quality guideline.

Norwood et al. (2003) conducted a literature review on the effects of metal mixtures. Mixtures varied from 2 to 11 metals. The investigators determined that the TU approach is presently the most appropriate model for predicting effects of metal mixtures, based on currently available data (e.g., effect concentrations, ECx values). Effect addition models, especially if based on body or tissue concentrations, might be more accurate in the future, but they require reliable dose-response and bioaccumulation curves for all single metals (not just ECx values) and then careful testing of the models (research on tissue concentration effect levels is ongoing).

Application of HSAB. The QICAR approach (described in Section 3.x Environmental Chemistry) might also be applicable to predicting the potential for interactions of metals in mixture. Unsatisfied with the qualitative conclusions of Newman and McCloskey (1996), Ownby and Newman (2003) fit binary metal mixture data derived from the Microtox assay to the following model of joint independent action (Finney, 1947):

$$\text{Predicted } P_{A+B} = P_A + P_B - P_A P_B$$

where P_{A+B} is the biological response to the metal mixture, expressed as a proportion, and P_A and P_B are the biological responses to A or B when present singly. This relationship would hold if

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the actions of the paired metals were independent. However, if the metals were not independent, the $P_A P_B$ term will deviate from its expected value of $zP_A P_B$ where z = 1. Assuming that paired metals with very similar binding tendencies are more likely to interact with the same biological ligands than are metals with very dissimilar tendencies, deviations of the z coefficient from 1 would reflect departure from complete independence of metal action. Figure 10 clearly shows that the more alike two metals are in their binding tendencies ($\Delta\beta$), the further the coefficient deviates from unity; the more similar the paired metals in mixture, the more they interact. HSAB theory allowed prediction of metal interactions in this model system.

3.4.3.2. Limitations

At the present time, the most appropriate approach for determining the toxicity of metal mixtures and addressing the two key questions detailed above is to use the TU approach as a screening-level assessment. This approach cannot, however, be used beyond screening because it does not provide certainty. Norwood et al. (2003) found that of 191 case studies examined, 70% were additive or less than additive. Thus, this approach was primarily either appropriate or overprotective, but 30% of the case studies indicated that this approach would be underprotective. For aquatic organisms acutely exposed to cationic metals, the assumption of additivity is sufficient, particularly if bioavailability adjustments are made using the BLM.

Currently, there are no realistic means of ranking mixtures of metals or individual metals within mixtures. National criteria for mixtures also are not possible at this time. Furthermore, the concentration addition (TU) approach is recommended only for application to mixtures with less than six components. This issue remains site specific because interaction responses are dependent on both the actual metal mixture combinations (metals and ratios) and the exposed organisms.

> Currently, the most appropriate approach for determining the toxicity of metal mixtures is to use the **Toxic Unit (TU) approach** as a screening-level assessment tool. This approach cannot, however, presently be used beyond screening, because it does not provide adequate certainty since combined effects depend on the relative amounts of each metal. Furthermore, the TU approach is recommended for applications with mixtures containing less than six components.

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Researchers are presently attempting to predict the effects of metal mixtures on the basis of critical body concentrations of metals. Ongoing research is attempting to integrate the effect accumulation functions of each metal into a metal mixture model in which an effect addition formula will be compared with a concentration addition formula, both based on body concentration. Current work is focused on aquatic invertebrates, and similar research is required for other organisms.

It is possible that the BLM may be expanded in the future to include mixtures. In theory, if two metals compete for binding to the same site of toxic action on an organism, it should be possible to model the total metal bound to that site and hence predict metal toxicity using a mechanistic BLM approach in an effects addition model. Alternatively, if two metals do not compete for the same binding site on the organism, then the BLM may provide more reliable estimates of individual metal bioavailability, and these estimates can then be combined in more accurate effects addition models. However, at present, these possibilities remain theoretical and need to be tested.

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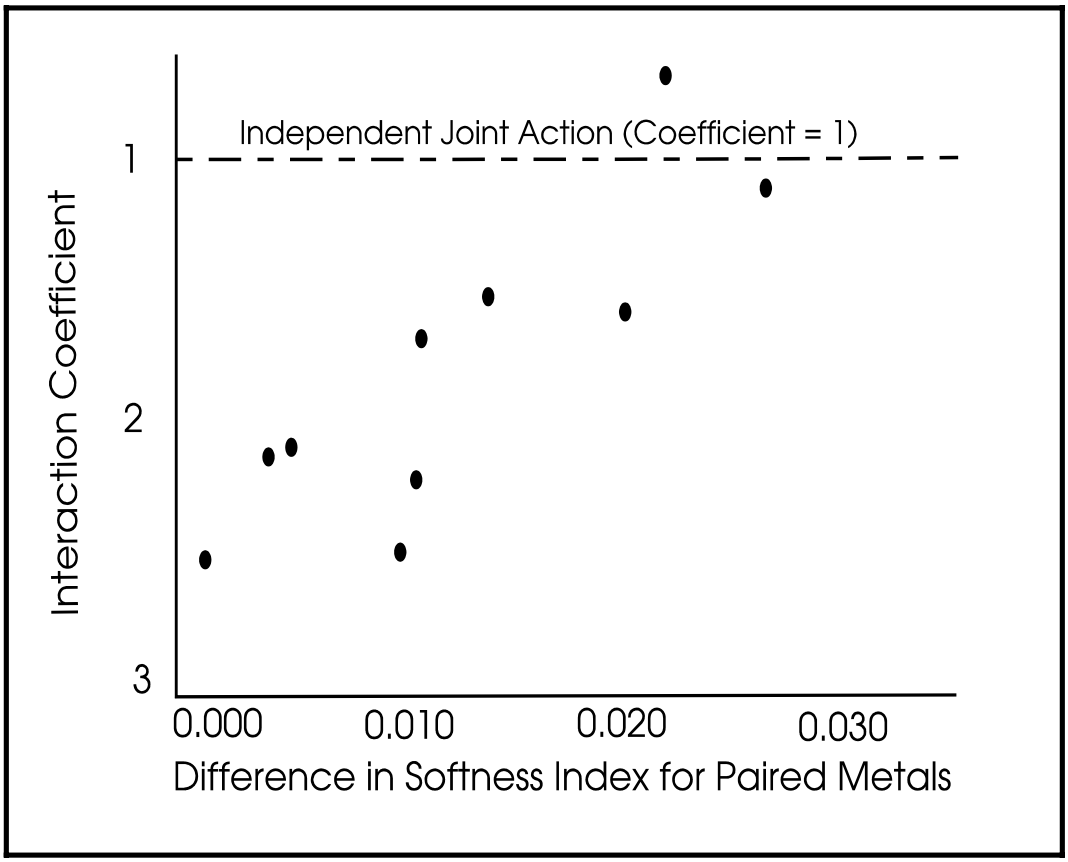

Figure 10. Binary metal mixture deviation from independent joint action can be predicted from the degree of similarity in binding tendencies for the paired metals (simple difference in metal Δβ values for the paired metals).

Source: Adapted from Ownby and Newman (2003) (Fig. 1).

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3.4.4. BACKGROUND

> ***Background*** is defined as the amount of metals occurring in soils, water, or air 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 man-made substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that are not specifically related to the release in question. Background can exacerbate toxicological effects and accumulations from direct emissions or other sources, or conversely it may result in adaptation of organisms to higher metal concentrations and result in increased tolerance to emissions.

Background is defined as the amount of metals occurring in soils, water, or air 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 man-made substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that are not specifically related to the release in question (U.S. EPA, 2003). Background must be defined in a specific spatial and temporal aspect that is related to the scope of the particular hazard or risk assessment. Background 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 (see above section). 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, so knowledge of background levels is not as significant.

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3.4.4.1. Application

Concentrations of metals in soils and waters of the U.S. vary tremendously. Thus, use of a single number to represent all areas within the U.S. is to be discouraged. State-wide averages (Table 2.3, US EPA, 2003) provide somewhat better resolution, but even these are constrained by political boundaries, not by geochemical characteristics. Additional information on concentration of metals in soils at smaller spatial resolutions is provided in Shacklette and Boerngen (1984). Some metals (e.g., Fe, Cu, Zn) are included in the State Soil Geographic Database (STATSGO) available at www.nrcs.usda.gov/technial/techtools/stat_browser.html. These data can be grouped at whatever spatial scale is required, but they are not screened for whether they represent true background concentrations. Similarly, data on water concentrations can be retrieved from EPA's STORET database (www.epa.gov/storet/index.html). These data must be used with caution, however, as this is a voluntary-entry database, and there is no consistent method for measurement or for QA/QC of the data. Like the STATSGO information, STORET data do not necessarily represent true background levels; additionally, there is incomplete coverage across the U.S.

Similar data for sediments are available from the EPA's National Sediment Quality Survey database, which is available in the form of an MS Access 1997 database and can be obtained on a CD from OST (Washington, DC). It contains survey data from 1980 to 1999, including sediment chemistry data, tissue residue data from selected organisms, and toxicity data (lethal and sublethal effects on various test organisms). Overall, there are data from more than 50,000 stations and 4.6 million analytical observations. The data were complied from a variety of sources, but mostly from state and federal monitoring programs, and sampling and analysis strategies varied among sources. All data have "data qualifiers" associated with them in the database. However, this was not a statistically designed survey, and is heavily biased toward contaminated sites, so inferences to areas that were not sampled should be made with caution.

A more appropriate approach is to define average (and ranges) of background concentrations for various ecoregions (Bailey, 1998; Hargrove and Hoffman, 1999; Omernick, 1986). Work is underway in this regard, but such values currently are not available. Therefore, the recommended default is to use state averages where possible and to always define the range

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that might be encountered within the spatial scale being considered. It is also important to recognize that background concentrations in water are highly variable through time, as flooding or drought conditions substantially change the relative concentrations of metals in a water body. Again, it is suggested that ranges rather than single number averages be used.

There are several practical issues to consider for evaluating the contribution of background to hazard or risk and its implications for various risk management options when conducting site-specific assessments. First, a physical and/or temporal boundary needs to be defined for the analysis. Next, background should be described, estimated, or measured. OSWER (2000, 2002b, c) provides detailed guidance on how to estimate local background concentrations and notes that locations of background samples must be areas that could not have received contamination from the site but that have the same characteristics as the medium of concern (i.e., water, soil, or air).

Another reason to include background in the assessment is to evaluate the effect of the remedial options. Although some areas of the site may have elevated concentrations for certain metals, other metals may not be elevated. Remedial actions could cause these naturally occurring metals to become more bioavailable, thereby resulting in unintended toxicity. The HSAB theories and QICAR models (see Section 3.x.x Environ. Chem) can be applied to derive useful estimates of biological activity for metals to aid in making decisions regarding remedial actions.

Added risk approach. How the information on background concentrations is used in the final risk assessment depends on how data on toxic responses were generated and the relationship of the bioavailability characteristic of the naturally occurring material to the source-related additional metal. For aquatic organisms, toxicity tests generally are conducted in waters that are relatively low in background metals and are of moderate hardness. Therefore, the toxicity thresholds described (e.g., in WQC) represent the total amount of metal in the water, not the amount that can be added to the natural background levels. If, however, the tests are run on site-specific waters where metal background and bioavailability may differ significantly from standard waters and where organisms have been acclimated to such conditions, then the toxicity threshold reported will be the amount that is added to the natural background. However, when using this approach, caution must be exercised, because the background levels of metals in the

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aquatic system may be highly variable over short time periods. The primary consideration is that the *bioavailable fraction* of the natural background concentrations should be added to the *bioavailable fraction* of the added metal.

In terrestrial systems, toxicity bioassays for soil organisms (plants and invertebrates) are conducted either in artificial soils or in actual soils, both of which contain background concentrations of metals (particularly of essential elements). Therefore, the toxic levels reported are the amount added during the study. Unfortunately, the background amounts frequently are not reported, so it may not be feasible to take a true "added risk" approach. Furthermore, the amount of metal added to the test system generally is in a much more bioavailable form (e.g., a metal salt) than is the background material. Therefore, for a site-specific release of a highly bioavailable form of the metal, the background concentration may not contribute significantly to total metal uptake. Thus, it becomes extremely important to measure exposure in terms of the *bioavailable fraction*, so field exposures can be expressed in a manner comparable to the highly bioavailable material used in toxicity tests for threshold setting.

For human health and wildlife assessments, the amount of metal in food material needs to be taken into consideration in a manner similar to that discussed above for soil organisms. Again, differences in bioavailability of food-incorporated metals and top-dressed metal salts must be considered. Additionally, natural uptake and the amount of metals in forage and other food items will vary, depending on the amount of metal in soil and the particular species of plant/animal present in the area. Site-specific assessments can take this into consideration. For national or large-scale assessments, a default assumption can be made that food items contain sufficient amounts of micronutrients to meet dietary needs and that the toxic threshold value represents the *bioavailable fraction* that is added above these values.

3.4.4.2. Limitations

National databases of metal concentrations in soil or water do not currently differentiate between naturally occurring levels and levels that are elevated due to anthropogenic sources. However, the databases can be screened to ascertain whether specific areas are impacted by point source emissions and so can be used as reasonable estimates for large-scale background levels.

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More importantly, however, is that background concentrations are most frequently reported as total amount of metal, without specifying the bioavailable fraction or chemical speciation or the data (e.g., pH or redox potential) needed to estimate bioavailability. Information on probable mid- to long-term changes in soil or water properties that might enhance bioavailability of background metals also needs to be provided for accurate assessments of future risk.

3.4.5. INDIRECT EFFECTS OF METALS

> ***Indirect effects*** to organisms initiated by metals toxicity can be negative (density dependent or independent) or positive (density dependent) and can occur between species or within the same species. Table 25 summarizes some of these relationships.

Metals can initiate ecological changes by directly affecting individual organisms (i.e., through toxic responses). Organisms can die, fail to reproduce, or have altered behavioral patterns. As a consequence of such actions on individuals, other organisms within the community will be indirectly affected through reduced number of prey items or predators or changes in competition for resources. Additionally, indirect interactions between organisms can and do occur independently of initiating effects from toxicity due to metals exposures (described by Dill et al., 2003). Although "initiators" may be biotic, physical, or chemical, in all cases there is an effect to a species (the "transmitter") that has an effect on another species (the "receiver").

Indirect effects to organisms initiated by metals toxicity can be negative (density dependent or independent) or positive (density dependent) and can occur between species or within the same species. Some examples are summarized in Table 18; additional examples are provided by Chapman et al. (2003). Interactive effects can also occur due to the combined effects of environmental stressors and metals toxicity. For instance, Liess et al. (2001) found that the toxicity of copper to an Antarctic amphipod was increased by food shortage and excessive ultraviolet-B radiation. Some authors have considered such interactive effects to be indirect; however, they can be addressed as direct effects in risk assessments and hence are not considered further.

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Table 18. Examples of Indirect Effects of Metal Toxicity

Transmitter organism	Receiver organism	Comment
Prey populations reduced	Predator populations reduced	Negative indirect effects due to reduced prey (food)
Predator populations reduced	Prey populations increased	Positive indirect effects due to reduced predation
Competitor populations reduced	Competitor populations increased	Positive indirect effects due to reduced competition
Toxicity to some larvae of a species	Increased adult-to-larval survival, increased growth and biomass of adults of the same species	Positive indirect effects due to density-dependent compensation

3.4.5.1. Application

Functional redundancy (species having similar roles in ecosystem processes) is a well-known but arguably not well-understood phenomenon in ecosystems. It is often assumed that if an organism's primary prey item is reduced or eliminated, then the organism can switch to another prey item due to functional redundancy. However, in the case of food web-mediated effects, the following sequence can and does apply: chronic metal exposure reduced; food abundance of certain dietary components; increased energetic costs of feeding; and reduced growth efficiency.

A determination of whether indirect effects such as loss of preferred prey can occur requires three components. First, appropriate conceptual diagrams need to be developed in the problem formulation phase of the risk assessment and subsequently refined. Such diagrams need to incorporate sufficient detail regarding key biotic interactions (competition, predation) and the ecological context in which the species exist and pollution occurs. As noted by Chapman et al. (2003), seasonal and life-stage changes in feeding patterns can occur and will "require iterative temporal diagrams showing the various reasonable possibilities."

Second, risk assessors should focus proactively on the first three possibilities in the table above, because it is extremely unlikely that indirect effects due to density-dependent compensation will be detectable without extraordinary effort. Increased numbers of receiver organisms due to reduced competition or predation are more likely to be detected and more likely

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to have overall adverse implications for communities and/or ecosystems, despite their apparent positive aspects (to the particular receiver species).

Third, risk assessors should focus on any cases of reduced growth of individuals, particularly where the individuals affected are relatively tolerant to metals toxicity *and* their normal feeding patterns are disrupted. These are clear indications (though not conclusive proof) of indirect effects of metals toxicity. An example of negative indirect effects due to reduced prey is provided by Campbell et al. (2003). These authors summarize extensive field research into yellow perch in metal-impacted lakes in eastern Canada. Yellow perch in lakes shift from feeding on zooplankton to feeding on littoral macrobenthos during their second year of growth, and then begin to include a significant amount of fish in their diet during their third to fifth year of growth. Fish in the most metal-impacted lakes did not undergo this normal sequence of diet shifts. Instead, they continued to utilize smaller prey throughout their lives, due to the loss of their primary prey species to direct metal toxicity. A bioenergetic bottle-neck developed because the perch's growth efficiency was reduced by the need to catch and eat smaller-sized prey. The perch were more tolerant to metals toxicity, and thus there were no major direct effects on their survival (though multiple physiological effects were recorded). However, the loss of their primary prey species resulted in smaller or stunted perch, a major indirect effect of metals toxicity.

3.4.5.2. Limitations

It is difficult to predict natural (e.g., behaviorally mediated), indirect interactions in nature (Dill et al., 2003). It is also difficult to predict indirect interactions due to abiotic factors such as metals toxicity. Accurate predictions require good understanding of the functional interactions between populations, particularly along food chains, as well as density-dependent and density-independent processes between and within species.

> Presently there is no realistic means of ranking metals on the basis of indirect effects, nor are national criteria possible. This issue remains a site-specific one because interactions between the initiator (metal toxicity), the transmitter, and receptor organisms are dependent on both the level and type of toxicity and the sensitivities of individual organisms within structurally and functionally unique populations, communities, and food chains.

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As noted by Campbell et al. (2003) and Dill et al. (2003), indirect effects of stressors on organisms probably are not uncommon occurrences. However**,** there are few documented cases of this occurring, and it is likely that most cases go unrecognized. It would be useful to review previous detailed-level ecological risk assessments involving metals toxicity to determine and document previous cases.

Indirect effects from metals toxicity are primarily associated with ecosystem function, not structure. However, ecological risk assessments typically are focused on determining risk to structure, not function. The assumption is made that measuring structure protects function because of functional redundancy. Clearly, given the reality of indirect effects, this is at best a questionable assumption that needs to be tested.

3.4.6. BIOAVAILABILITY IN TERRESTRIAL SYSTEMS

Bioavailability issues for terrestrial organisms are closely linked to soil physical and chemical parameters. As discussed in Section 3.1, there are qualitative and quantitative methods and models for considering soil chemistry issues and aging of metals in soil that relate to metal bioavailability and its toxicity in soil. Unless such determinants of soil loading capacity, aging of metals, and speciation in soil solution are considered, accurate estimates of exposure to the terrestrial biota cannot be made. In situations where information is not available, it is recommended that bulk soil chemistry be used with a default of 100% bioavailability.

> Unless soil physical and chemical parameters, such as soil loading capacity, aging of metals, and speciation, are considered, accurate estimates of exposure to terrestrial biota are not possible. In these situations where information are unavailable, it is recommended that bulk soil chemistry be used with a default of 100% bioavailability.

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3.4.6.1. Soil Organisms: Invertebrates and Microorganisms

Metal speciation is the primary consideration in assessing the bioavailability of metals to soil invertebrates and microbes. Major assumptions regarding metal exposure in aquatic systems, such as a the relatively homogenous dissolution of metals in the exposure water, may not be applicable or may apply at different scales in soil systems. Although soil microbes may be immersed in soil solution films surrounding soil particles, few invertebrates are exposed to metals in this manner. Exposure usually consists of partial contact of soil solution films with the surfaces of the invertebrates that are capable of absorbing metals (e.g., earthworm dermal surfaces). Direct contact with membranes across which metal uptake can occur does not take place for many hard-bodied soil invertebrates (e.g., arthropods), and metal uptake is almost entirely through the ingestion of metal associated with particle matter or soil solution. For these reasons, exposure and the relative bioavailability (RBA) cannot be expressed similarly for each organism in the soil ecosystem, and an understanding of primary routes and mechanisms of metal exposure must be established for species or groups of similar organisms.

> ***Metals speciation*** is the primary consideration in assessing the bioavailability of metals to soil invertebrates and microbes.
>
> Often, direct toxicity testing of the soil of concern is the best method for assessing bioavailability and toxicity-to-soil biota. Issues such as spiking of metals solutions onto soils, aging, and laboratory-to-field extrapolation need to be considered.

Often, direct toxicity testing of the soil of concern is the best method for assessing bioavailability and toxicity-to-soil biota. Issues such as spiking of metals solutions onto soils, aging, and laboratory-to-field extrapolation need to be considered. In the ecological soil screening document (U.S. EPA, 2003), published literature was evaluated using primary soil parameters affecting lability of metals in soils in a matrix to qualitatively indicate metal bioavailability. Further information on this topic and factors relating soil chemistry to soil biota toxicity are discussed in Sections 3.1. A terrestrial BLM method currently under development (Allen, 2003) will provide a useful tool to link bioavailability, soil chemistry, and toxicity to soil biota.

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3.4.6.2. Plants

The most common route of metal exposure in plants is through the roots. Ions and organic molecules contact roots via the transpiration stream, diffusive transport, and microbe-facilitated transport. At the root surface, soluble contaminants have the potential to enter into the root tissue through the transpiration stream or through a range of mechanisms that are designed to facilitate nutrient uptake. In general, it is thought that only uncomplexed, free ionic species of cations and ions can be taken up by roots. This has been described using a free ion activity model (FIAM; Lund, 1990; Parker and Pedler, 1997). Sauvé et al. (1998) put forward a method to calculate free metal activity levels for copper and lead to derive a pH-dependent soil criteria for soil biota. The soil criteria paper was based in part on previous studies (Sauvé et al., 1995, 1997a, b; McBride et al., 1997) to generate models to predict free copper activity from total metal content, pH, and organic matter content or, in the case of lead, using only total metal levels and pH. The equations were generated from more than 60 soils using ion selective electrodes and standard methods for determining pH, organic matter content, and total metal levels. However, exceptions to this model have been identified. Ionic or organometallic complexes that increase the total concentration of elements at the root surface have been correlated with increased uptake, either through disassociated ions or through uptake of intact complexes (McLaughlin et al., 1994: Parker et al., 2001). In addition, it is not clear how well plants can distinguish between ions of similar size and charge. Plant uptake of macronutrients is much better understood than is uptake of micronutrients or toxic metals, with the primary work on uptake of micronutrients focusing on iron (Welch, 1995). Chaney (1980) and Chaney and Ryan (1993) discuss the plant-soil barrier as a mechanism that limits the availability of some metals to plants. This tool can remove several metals from consideration in risk assessments.

Plant bioassays can be used to measure the RBA of metals in various soil types. Results can be used to determine either the direct or the indirect value of bioavailability of contaminants in plants and to extrapolate an indirect estimate of RBA to organisms that consume the plants (assuming a correlation between plant and animal uptake). This type of testing has been routinely done in agriculture for decades and has been used to validate extraction tests. Tests

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have most often focused on identifying plant deficiencies of particular elements, but they are easily adapted to evaluate toxicities (Gettier et al., 1985).

In the absence of test data, RBA can be estimated qualitatively based on relative pH and organic matter content (Tables 19 through 21; from U.S. EPA, 2003). Although other soil factors can be significant, most notably cation exchange capacity (CED). However, combinations of these two soil parameters and their ranges are sufficient as a qualitative guide for assessors to identify soils where metals may have increased (or decreased) availability to plants.

Table 19. Qualitative Bioavailability of Metal Cations in Natural Soils to Plants

	Soil pH		
Soil type	**Low organic matter (<2%)**	**Medium organic matter (2 to <6%)**	**High organic matter (6 to 10%)**
4 ≤ Soil pH ≤ 5.5	Very high	High	Medium
5.5 < Soil pH ≤ 7	High	Medium	Low
7 ≤ Soil pH ≤ 8.5	Medium	Low	Very low

Table 20. Qualitative Bioavailability of Metal Cations in Natural Soils to Soil Invertebrates

	Soil pH		
Soil type	**Low organic matter (<2%)**	**Medium organic matter (2 to <6%)**	**High organic matter (6 to 10%)**
4 ≤ Soil pH ≤ 5.5	Very High	High	Medium
5.5 < Soil pH ≤ 7	High	Medium	Low
7 ≤ Soil pH ≤ 8.5	Medium	Low	Very Low

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Table 21. Qualitative Bioavailability of Metal Anions in Natural Soils

Soil type	Soil pH		
	Low organic matter (< 2%)	**Medium organic matter (2 to <6%)**	**High organic matter (6 to 10%)**
4 ≤ Soil pH ≤5.5	Medium	Low	Very Low
5.5 < Soil pH < 7	High	Medium	Low
7 ≤ Soil pH ≤ 8.5	Very High	High	Medium

Source: U.S. EPA (2003).

3.4.6.2.1. Critical Tissue Residues

When used appropriately, plant tissue analysis can provide an indirect, semiquantitative assessment of bioavailability processes (NAS, 2002). For phytotoxic metal concentrations to be effectively used as an indirect measure of bioavailability, it is important that the threshold values of the plant tested be well understood. In addition, toxicities of certain metal elements are associated with deficiencies of others. For example, increased zinc, copper, and nickel toxicities can be associated with iron deficiencies (Bingham et al., 1986), and increased lead and zinc toxicities can also be related to phosphorus deficiencies (Laperche et al., 1997; Brown et al., 1999, 2000). The behavior of plant species in response to nutrient deficiencies varies, and this behavior can affect the uptake of potentially toxic metal elements (Marshner, 1998). Because of these multiple confounding factors, the bioavailability of metals in plants (as well as to consumers) is more accurately and reliably measured directly as the edible plant tissue concentrations of the metal in association with soil metal concentrations in the root zone (NAS, 2003).

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3.4.6.3. Wildlife

For many contaminants (including most metals), the dietary intake pathway is the main route of exposure for wildlife (NAS, 2002; see also Section 3.3). However, the incidental ingestion of soil can often contribute to the majority of exposure for a wildlife consumer. Because many inorganic metals do not readily accumulate in food, highly contaminated soil may result in higher exposures to metals through activities such as grooming fur, preening feathers, consuming soiled prey or forage, burrowing, and taking dust baths. However, canopy feeders would be anticipated to have less incidental soil ingestion and therefore less exposure to inorganic metals than wildlife that consume food that is in more intimate contact with the ground.

The relative importance of the dietary and incidental soil ingestion pathways is dictated by (1) the fraction of total metal available in soil versus that in food and (2) the RBA of the metal in the soil as compared to metal in food items. Table 13 in Section 3.2.3.4.3. shows the relative contribution of food and soil before accounting for bioavailability. Understanding of the bioavailability of metals in incidentally ingested soils becomes necessary when there is a high amount of metal in the soil that is not taken up by soil organisms (plants or invertebrates). However, the same variables that restrict uptake by plants or other soil organisms act to reduce bioavailability to wildlife that ingest soil directly. Therefore, a qualitative estimate of low RBA could be made for these soils. Furthermore, RBA data that are generated for human health studies could be used to estimate soil bioavailability for wildlife, acknowledging the uncertainty inherent in such interspecies extrapolations.

Dietary bioavailability. Very little information is available on dietary bioavailability for most wildlife species (see TN&A and Menzie-Cura, 2001 for a review, cited in NRC, 2002). One of the most significant challenges is that the bioavailability of metals may be influenced by differences in digestive physiology and anatomy across the broad and diverse range of mammalian and avian species. For example, metals present in soils may be more or less bioavailable within the gut of an herbivore that relies on fermentation as compared to the comparatively simpler gut of a carnivore that is designed to break down proteins. These gut systems differ in chemistry (including pH) and residence time. The potential differences between

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species have not yet been explored rigorously. In general, ruminants absorb lower amounts of metals than do monogastric animals such as rats (NRC, 1980). Some general guidelines are provided for some metals (e.g., lead) in NRC (1980), and human-derived values can be used as default values in the absence of species-specific data.

Critical body residues (CBRs). CBRs are internal concentrations of chemicals that are correlated with the onset of a toxic response (Lanno et al., 1998; Conder et al., 2002). The use of CBRs reduces uncertainties in ecological risk assessment procedures because they account for site-specific bioavailability (Van Wensem et al., 1994; Van Straalen, 1996). CBRs can be based on whole-body residues (see below for discussion of this approach in soil invertebates) or concentrations in specific tissues. Tissue-specific critical loads (such as for lead in the liver or cadmium in kidneys) have been established for several species of vertebrate wildlife for lead (in liver), cadmium (in kidney), selenium (in eggs), methyl mercury (in brains) (See Beyer et al., 1996, for these figures).

3.4.7. BIOACCUMULATION IN TERRESTRIAL ORGANISMS

For terrestrial ecosystems, the concept of bioaccumulation is intended to capture the potential for two ecologically important outcomes: 1) direct toxicity to plants and wildlife; and 2) secondary toxicity to animals feeding on contaminated plants and animals. This approach captures the potential for trophic transfer of metals through the food web, so total exposure can be calculated, including dietary intake as well as intake from contaminated environmental media (soil and water). For vegetation, the BAF (or BSAF) is defined as field measurements of metal concentration in plant tissues divided by metal concentration in soil (or soil solution); the BCF is defined as the same measurement carried out in the laboratory (Smolders et al., 2003).

BAFs for plants include metals aerially deposited on leaves as well as those in soil particles adhering to roots. Such metals will not be part of BCFs, which frequently are determined in hydroponic culture. Similar differences between BCFs and BAFs apply for earthworms exposed in laboratory studies using the filter paper substrate protocols. Furthermore, BCFs with earthworms may not include additional feeding of the animals during the study.

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Additionally, field studies are reflective of chronic exposures, whereas BCFs may be calculated from shorter time frames. For birds and mammals, whole-body BAFs generally are not calculated, except for small mammals such as rodents (Sample et al., 1998b). ; rather, concentrations in target tissues are measured for comparison with critically toxic levels (Beyer et al., 1996).

The BAFs for metals by soil invertebrates and most plants are typically <1, although they usually are based on the total metal in soil and tissue. Biota-to-sediment accumulation factors (BSAFs) expressed in this manner may be suitable for comparisons of metal uptake within the same soil type, but they would be misleading if soil bioavailability factors (e.g., pH, organic carbon) differ. Unfortunately, the literature database is populated almost entirely with BAFs derived from measurements of total metal. In the future, a ratio of total metal in the organism to some measure of the bioavailable fraction of metal in the soil (e.g., free ion concentration, weak salt extractable) should be used for expressing a BSAF that allows comparison among different soils. An alternative approach currently under study is to use a multivariate statistical model to look for patterns of uptake of multiple metals in order to predict the potential bioconcentration of one of particular interest (Scott-Fordsmand and Odegard, 2002).

> ***Bioaccumulation*** can be defined as the net accumulation of a metal in a tissue of interest or a whole organism that results from exposure. Metal bioaccumulation can apply to the entire organism, including both metal adsorbed to surfaces or absorbed by the organism or to specific tissue. It is usually expressed on a weight (dry or wet)- adjusted basis. The bioaccumulation of metals arises from all environmental sources, including air, water, solid phases (organic and inorganic phases in soil and sediment), and diet and also represents a steady-state balance of losses from tissues and the body.

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3.4.7.1. Models for Bioaccumulation in Soil Inverterbrates

3.4.7.1.1. Application

3.4.7.1.1.1. *Univariate Models*. The bioaccumulation of metals in soil organisms cannot reasonably be modeled from information based solely on soil concentrations. Therefore, models for the prediction of metal bioaccumulation by soil invertebrates are primarily empirical in nature, describing relationships between metal body burdens in oligochaetes and collembola, soil metal concentrations, and soil physical/chemical characteristics. Statistical relationships have been established using univariate and multiple regression approaches. Sample et al. (1998) and Peijnenburg et al. (1999b) have each developed univariate uptake models for earthworms that are based on empirical data (metal concentrations in worms vs. the natural log of amount of metal in soils) that are widely used as a first approximation. However, these models are not specific to soil type and therefore do not account for bioavailability factors such as pH, clay content, or cation exchange. Furthermore, they do not adequately predict Cr or Ni uptake. Similar empirical uptake models are available for small mammals (U.S. DOE, 1998b).

> The bioaccumulation of metals in soil organisms cannot be modeled from information based solely on soil concentrations. Two types of models are available to help describe the relationships between metals body burden and soil parameters: 1) ***univariate models*** that describe statistical relationships between body burdens, soil metal concentrations, and soil physical and chemical properties, and 2) ***multivariate models*** that explain BAFs as a function of soil properties.

3.4.7.1.1.2. *Multivariate models*. Multivariate models also are available (Peijnenburg et al., 1999a, b) for *Eisenia andrei* and *Enchytraeus crypticus* that explain BAF as a function of soil characteristics. The soil parameters that generally contributed the most to explaining the variance between uptake rate constants and BAFs were pH (for Cd, Zn) and also CEC (for Pb) and clay content (for Cd). Similar studies are needed for describing relationships between soil physical/chemical characteristics and metal bioaccumulation in other groups of soil invertebrates such as collembola and isopoda. Until these are available, the models for earthworms and

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enchytrids can be applied to other groups, although the addition of a small uncertainty factor may be warranted.

Path analysis has been suggested as an alternative for multiple regression in describing these relationships. It partitions simple correlations into direct and indirect effects, providing a numerical value for each direct and indirect effect and indicates the relative strength of that correlation or causal influence (Basta et al., 1993). Bradham (2002) used path analysis and backwards stepwise regression analysis to derive statistical models capable of predicting uptake and effects of As, Cd, Pb, and Zn in earthworms as a function of soil properties.

Saxe et al. (2001) described a model for predicting whole-body concentrations of Cd, Cu, Pb, and Zn in *Eisenia andrei* as a function of pH, soluble metals in the soil at gut and environmental pH, and soluble organic carbon in soil extracts. The model also includes parameters that characterize the ability of worms to regulate the metal body burden, whether metal uptake is via the epidermal or gut surface and whether the metal is essential. The model has been validated against a series of Dutch soils and is very good at correctly predicting metal accumulation.

3.4.7.1.2. Limitations

Bioaccumulation of organic substances is typically modeled using a one-compartment, first-order kinetics (1CFOK) model. However, most of the assumptions of the model are violated when applied to bioaccumulation of metals by soil invertebrates. Soil invertebrates are not exposed to a constant concentration of metals in the soil over space and time, making it difficult to accurately define exposure. Sufficient data exist on the metabolism of metals to show that all pools of metal taken up by the soil invertebrates are not equally available for depuration (some are actually never depurated and are released only when the organism dies), making a 1CFOK model an inaccurate approximation.

Metal concentrations do not reach a steady state that is proportional to external (i.e., soil) concentrations. This is similar to the situation in aquatic systems where metal bioaccumulation is a function of soil concentration. Internal essential metal concentrations are regulated and remain relatively constant over a wide range of soil metal concentrations. Only when normal regulatory mechanisms are overwhelmed do internal levels of essential metals increase.

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Accumulation of nonessential metals also violates the assumption of steady state, as organisms have evolved mechanisms for the detoxification of nonessential metals that involve the internal accumulation of the metal in forms that are not toxic to the organism (e.g., incorporation into inorganic granules or binding to organic molecules to form metal ligands such as metallothioneins).

3.4.7.2. Critical Body Residues

CBRs are an extension of the concept of bioaccumulation to internal concentrations of metals that are correlated with some toxic response and hence represent toxicological bioavailability (Lanno et al., 1998; Conder et al., 2002). Use of CBRs in appropriate species may reduce uncertainties in ecological risk assessment procedures (Van Wensem et al., 1994; Van Straalen, 1996). However, only a few CBRs have been developed in soil invertebrates for metals. Crommentuijn et al. (1994, 1997) and Smit (1997) established CBRs for sublethal effects for Cd and Zn, respectively, in the springtail (*Folsomia candida*). Conder et al. (2002) demonstrated that effects of Cd in earthworms (*Eisenia fetida*) are correlated with concentrations of the metal in the solid phase of the worms (i.e., the pellet fraction, following homogination and centrifugation). If future research can isolate the fraction of an invertebrate that represents toxicological bioavailability, then it may be possible to estimate a toxicological BSAF representing a relationship between a specific fraction of metal that accumulates in the organism and a measure of chemical bioavailability in the soil. Until then, CBRs based on whole organism analyses are a reasonable approximation for use in ecological risk assessments.

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3.4.8. AQUATIC TOXICITY

Several variables affect the outcome of a laboratory toxicity assay, including the acclimation of test animals to the culture conditions (see Section 3.4.2. Acclimation for further discussion), the natural background concentrations of the metals (including, but not limited to the metal of interest) in either the test water or the site of concern (see Section 3.4.4. Background), potential interaction of the various metals (see Section 3.4.3. Mixtures), and the bioavailability of the metal (and its potential to transform to bioreactive species; see Section 3.1. Environmental Chemistry). Knowing the species of metal that is likely to be present in the environment is a necessary prerequisite for successful comparison of effect levels derived from laboratory tests to predicted exposures.

> Knowing the species of metal that is likely to be present in the environment is a necessary prerequisite for successful comparison of effect levels derived from laboratory tests to predicted exposures.
>
> Variables that may potentially affect the outcome of laboratory toxicity assays include acclimation of test animals to culture conditions, natural background concentrations of the metal (including, but not limited to the metal of interest), potential interactions of the various metals, and the bioavailability of the metal along with its potential to transform to bioreactive species.

Only a limited number of metal species are considered to interact at the biochemical/physiological site of action. Additionally, the fraction of the total metal that is present in these bioreactive forms may vary markedly with water quality, representing only a small fraction of the total concentration of metal. The free metal ion is viewed as being the principal bioreactive form, although it is not necessarily the only one (Campbell, 1995). Once a metal has entered the organism via dietary intake, it may change its form or be present in a variety of species. This leads to a continuing need to consider the form of the metal that is present within the organism when assessing the potential for effects (e.g., Winge et al., 1974).

3.4.8.1. Application

Computational models (e.g., the aquatic BLM (aBLM); discussed in the next subsection) were developed to account for differences in concentrations of bioactive metal species when assessing acute effects of metals (U.S. EPA, 1999a). The aBLM was based on principles

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originally outlined in terms of the FIAM (Morel, 1983; Campbell, 1995). The approach has broad appeal, and many stakeholders are working to further its development (see Paquin et al., 2002a, for a detailed overview of the historical development of the BLM and Gorsuch et al., 2002, for a compilation of manuscripts that describe many of the more recently completed and ongoing efforts). It considers

- Total metal concentration in the water column, the chemical speciation of the metal, and complexation of the metal by competing inorganic and organic ligands,

- The interactive effects of the bioreactive forms of the metal (e.g., the free metal ion and perhaps other metal species) with other cations that may compete for binding at sites of uptake or toxicity, and

- Accumulation of metal by the organism, including but not limited to accumulation at the site of toxic action.

The essence of the aBLM is that it is not the form of the metal in the water that is of ultimate importance, but the level of metal accumulation at the site of action. Hence, in the context of the aBLM, this site of action of toxicity (e.g., the gill) as a reactive biotic ligand that has a prescribed concentration (i.e., binding site density) and metal binding strength (characterized by a Log K value) that control the level of accumulation of the metal. The computations that are performed are consistent with those performed by any of a number of chemical equilibrium models (e.g., MINTEQ, MINEQL, etc.), with the key output being the concentration of the metal-biotic ligand complex (M:BL). The M:BL concentration is key, because this accumulation level at the proximate site of action of toxicity is assumed to be uniquely associated with a fixed biological effect (U.S. EPA, 1999a; Di Toro, 2001). The requisite chemical speciation calculations in prior aBLM applications have often been performed by the CHESS model (Santore and Driscoll, 1995) and employed metal-organic matter interactions patterned after those developed for the WHAM (Tipping, 1994). However, use of these particular models is not a necessary requirement of the aBLM (e.g., McGeer et al., 2000).

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An approach for extending the applicability of the BLM to chronic toxicity is use of the Ion Balance Model (Paquin et al., 2002a, b,c). The model uses the BLM to predict accumulation levels at the biotic ligand and then explicitly represents the degree of the physiological response of the organism to metal exposure over time (i.e., disruption of ionoregulation and gradual loss of plasma sodium). Although the approach, which was initially applied to silver, may ultimately provide a way to predict effects due to metals over varying exposure durations, further development and testing is required.

The selection of species used in the derivation of WQC for metals (and, therefore, for the aBLM as well) is based on historical and practical factors, most notably ease of culture under laboratory conditions. Plant testing follows a similar history, primarily based on routine testing required for pesticide registration and, consequently, includes many domestic crop species (e.g., lettuce). Wildlife testing has been done routinely only for pesticide studies (with the mallard, *Anas platyrhynchos*, and the bobwhite quail, *Colinus virginianus*). Soil invertebrate species have also been selected on the basis of ease of culture, although, as with the aquatic test species, an attempt has been made to be representative of different trophic levels and body types (hard vs. soft-bodied). Nevertheless, the list of species typically used in routine laboratory toxicity tests is necessarily only a small subset of species that are potentially exposed to contaminants in the environment. Because the selection of test species is not a random subsample of all species, extrapolation among species is potentially a large source of uncertainty in hazard or risk assessments.

Responses of aquatic organisms to metals vary significantly among taxonomic groups. For example, although most mayflies (Ephemeroptera) are generally sensitive to metals, caddisflies (Trichoptera) and many stoneflies (Plecoptera) are relatively tolerant (Clements et al., 1992). In fact, these species-specific differences in sensitivity to contaminants have motivated the development of numerous indices of water quality that are based on composition of benthic communities (Hilsenhoff 1987; U.S. EPA 1989; Barbour et al., 1992). However, because responses of aquatic organisms to chemical disturbances are usually contaminant specific (Slooff, 1983), field assessments of metal effects may be difficult when more than one contaminant is present, and caution is required when using biotic indices to assess effects of complex effluents.

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In some situations, it may be necessary to either develop chemical-specific indices on the basis of sensitivity to specific classes of contaminants or calibrate metrics used in individual field assessments.

Because aquatic organisms differ greatly in their sensitivity to contaminants, natural variation in community composition and abundance of dominant taxa between locations will influence results of field assessments. For example, metals discharged into a system dominated by highly sensitive taxa (e.g., heptageniid mayflies) will have greater effects than the same effluent discharged into a system dominated by tolerant organisms (e.g., chironomids). Kiffney and Clements (1996) showed that benthic communities from headwater streams were more sensitive to metals than were communities from mid-elevation streams. These results show that criteria protective of mid-elevation streams may not be protective of headwater streams.

An approach to extrapolating toxic responses to one metal to potential effects of a nontested metal is the quantitative HSAB-based relationships explored by Newman and co-workers in a series of publications (1996 to 2003). The QSAR-like models developed for metals are the QICARS. The approach was recently integrated into the general context of modern QSAR practices by McKinney et al. (2000). Lewis et al. (2000) extended the QICAR theme to rodent mortality, and Weltje (2002) successfully applied it to the Lanthanides. The QICAR approach is best applied with a full understanding of the system under study. It also may be possible to use such a QSAR approach to extrapolate potential effects from one biota to another for the same metal, although this requires further investigation.

3.4.8.2. Limitations

Currently, the aBLM data are limited to fish and to only a subset of metals (Cu, Ni, Cd, Ag). Work is underway that will soon provide data for application of the aBLM to invertebrates (e.g., *Daphnia*). Furthermore, the aBLM currently is applicable only to acute exposures. A chronic aBLM is under development, but it requires significant new knowledge about dietary toxicity of metals to fish and aquatic invertebrates.

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3.4.9. BIOAVAILABILITY IN AQUATIC SYSTEMS

3.4.9.1. Biotic Ligand Model (BLM)

The BLM is a recent attempt to develop a bioavailability model for metals with the latest information on the chemistry and physiological effects of metals in aquatic environments (Paquin et al., 1999; Di Toro et al., 2001; Santore et al., 2001). Like the FIAM and GSIM, the BLM is based on a description of the chemical speciation of metals in aqueous systems. Chemical speciation is simulated as an equilibrium system that includes complexation of inorganic ions and NOM. The chemical system is simulated by the chemical equilibria in soils and solutions (CHESS) model (Santore and Driscoll 1995), including a description of metal interactions with NOM based on the WHAM (Tipping, 1994).

A significant advantage of the NOM chemistry developed for WHAM is that the reactions and parameter values were developed by simultaneously considering numerous NOM samples and numerous metals. This approach provides a reasonably good description of NOM chemistry for water from diverse geographic regions and includes a pH-dependent formulation that considers competitive cation and ionic strength effects. Several other models are available for calculation of trace metal speciation in natural waters, including MINEQL (Westall et al., 1976; Schecher and McAvoy, 1994), MINTEQA2 (Brown and Allison, 1987), and PHREEQ (Parkhurst, Thorstenson and Plummer, 1980).

The BLM also includes reactions that describe the chemical interactions of metals and other cations to biological surfaces that correspond to the proximate site of action for toxicity of the metal. The model parameters define the degree of interaction on the basis of the binding affinity characteristics measured in gill-loading experiments (Playle et al., 1993a, b). That is, the biotic ligand (i.e., the gill) is represented by having a characteristic binding site density and conditional stability constants for each of the dissolved chemical species with which it reacts. Predictions of metal toxicity are made by assuming that the dissolved metal LC50, which varies with water chemistry, is always associated with a fixed critical level of metal accumulation at the biotic ligand. This fixed level of accumulation at 50% mortality is the concentration of the metal-biotic ligand complex (Me:BL) that is associated with 50% mortality, referred to as the

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LA50, for a fixed exposure. It is assumed to be constant, regardless of the chemical characteristics of the water (Meyer et al., 1999, 2002). This combination of reactions that describe aqueous metal speciation and organism interactions allows the BLM to predict toxicity to a variety of organisms over a variety of water quality conditions (Santore et al., 2001).

One significant advantage of the BLM is that most of the parameters are invariant for different organisms. Despite the complexity of the modeling framework, the thermodynamic constants used to simulate the inorganic and organic chemical equilibrium reactions are determined by the characteristics of the metal and available ligands. As such, the constants do not change for simulations involving different organisms. Although most BLM parameter values (including the biotic ligand binding constants and site densities) are consistent across organism types, differences in sensitivity across organisms types must still be accounted for. This is accomplished by adjusting the critical biotic ligand concentration (e.g., LA50) values for each species.

3.4.9.1.1. Applications

The BLM's ability to incorporate metal speciation reactions and organism interactions allows for the prediction of metal toxicity to a variety of organisms over a wide range of water quality conditions. Accordingly, the BLM is an attractive tool for deriving WQC in EPA's water program. Application of the BLM may eliminate the need for site-specific criteria modifications, such as water effect ratios, which are currently used to account for site-specific chemistry influences on metal toxicity.

Most of EPA's current WQC for metals account for differences in bioavailability through use of empirical relationships of toxicity to water hardness.

> The ability of the BLM to incorporate metal speciation reactions and organism interactions allows for the prediction of metal toxicity to a variety of organisms over a wide range of water quality conditions. Accordingly, the BLM is an attractive tool for use by EPA in deriving water quality criteria (WQC), and is currently being used to develop a freshwater aquatic life criteria criterion maximum concentration (CMC) for copper. EPA has developed a draft criteria document for copper that will undergo peer review. When EPA solicits scientific views from the public on the draft criterion, the model will be made available on the EPA/OST Web page at www.epa.gov/waterscience.

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These criteria combine the effects of various water quality variables correlated with hardness. Such criteria are most applicable to waters where these correlations are similar to the data set used to derive the relationships. EPA is now considering the use of the BLM (Di Toro et al., 1999) for development of aquatic life criteria for metals. The BLM is based on the premise that toxicity is related to metal bound to a biochemical site (the biotic ligand, such as the gill) and that binding is related to total metal concentrations and complexing ligands in the water. The complexing ligands compete with the biotic ligand and other cations in the water for binding to the free metal ion. Unlike the empirical harness relationships, the BLM explicitly accounts for individual water quality variables, it is not linked to a particular correlation among these variables, and it can address variables that have not been included in the hardness relationship.

Example: application of BLM to development of aquatic life criteria for copper. EPA currently is using the BLM to develop a freshwater aquatic life criteria criterion maximum concentration (CMC) for copper. As stated above, the BLM accounts for all important inorganic and organic ligand interactions of copper and also considers competitive interactions that influence binding of copper at the site of toxicity. Although a new model is being used, the criterion derivation is still based on the principles set forth in the 1985 guidelines (Stephen et al. 1985). To develop a BLM-based criterion, model predictions of critical accumulations on the biotic ligand (LA50 values) and either LC50 or EC50 values are needed to calculate species mean acute values (SMAVs) and genus mean acute values (GMAVs) as well as to derive a species sensitivity distribution.

Model input parameters. To predict copper accumulation on the biotic ligand the necessary water quality input parameters are:

- pH,
- DOC in mg C/L,
- Percent humic acid,
- Temperature,
- Concentrations of the major cations calcium, magnesium, sodium, and potassium (Ca+, Mg+ , Na+, and K+),

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- Concentrations of the major anions sulfate and chloride (SO4-, Cl-),
- dissolved inorganic carbon (DIC in mg HCO_3 /L),
- sulfide concentration, and
- copper concentration (e.g., dissolved LC50 in ug/L)

To predict copper toxicity, the same input parameters are necessary, and a critical biotic ligand accumulation value that can be specified or a model default biotic ligand critical accumulation value can be used to run the model. Acute copper toxicity data and the aforementioned input water chemistry parameters available from the literature are summarized. Studies lacking measured copper concentrations (i.e., only nominal values are reported) are not used in the evaluation.

Much of the aquatic toxicity literature reviewed for derivation of the copper criterion neither measured nor reported many of the key BLM input parameters, in which case they were estimated. A detailed description of the methods used to obtain or estimate these input parameters is included in U.S. EPA (2003a). Briefly, when critical water chemistry parameters were not available, authors were asked to measure missing water chemistry parameters in the toxicity test source waters. If primary authors could not be contacted, an attempt was made to contact secondary authors or personnel from the laboratories where the studies had been conducted. If data could not be obtained in this manner, the U.S. Geological Survey's National Stream Quality Accounting Network (NASQAN; http://water.usgs.gov/nasqan/) and the EPA STOrage and RETrieval (STORET; http://www.epa.gov/STORET/) data were used to obtain data for tests conducted in ambient surface waters.

Where actual water chemistry data were unavailable, data from other studies with the same water were used as surrogate values, if appropriate. In some instances, other sources were contacted to obtain water chemistry data (e.g., city drinking water treatment officials). The above-mentioned data were evaluated for representativeness and usefulness in estimating surrogate values for the dilution and/or test water used in the original studies. Where the above sources could not be used, geochemical ion input parameters for the BLM were based on the reported hardness measurement and regression relationships constructed from NASQAN data.

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Quality ranking of water chemistry input parameters. A ranking system of 1 to 6 was devised to evaluate the quality of the chemical characterization of the test water (but not the overall quality of the study). Studies that included all of the necessary BLM input parameters, based on measurements from either the test chambers or the source water, were assigned a ranking of 1. Rankings of 2 to 4 were assigned to studies that did not measure all parameters but provided reliable estimates of ion concentrations. Studies were assigned a ranking of 5 to 6 when one of the key parameters (DOC, Ca, pH, alkalinity) was not measured and could not be reliably estimated or if two or more key parameters (DOC, Ca, pH, alkalinity) were not measured. Only those studies with a rank of 1 to 4 were used to derive the criterion.

As with any modeling effort, the reliability of model output depends on the reliability of the input. Although the input data have been extensively scrutinized and filtered, the reliability of the BLM-derived values developed for copper in this project are subject to the limitations of the input measurements/estimation procedures described above.

Criteria generation. To calculate an acute criterion or CMC, reported acute toxicity values (e.g., LC50s) and individual test water chemistry parameters were used to calculate LA50 values by running the model in the speciation mode. These LA50 values were then "normalized" to a standard water condition by running the model in the toxicity mode and specifying user-defined LA50s. These normalized LC50s were used to calculate SMAVs, GMAVs, and a final acute value (FAV) pursuant to the 1985 guidelines procedure. The FAV represents a hypothetical genus more sensitive than 95% of the tested genera. The FAV was derived from the four GMAVs that have cumulative probabilities closest to the 5th percentile toxicity value for all the tested genera. Inputting this FAV as an LC50 concentration and running the model in speciation mode determines the lethal accumulation associated with the FAV in the standard test water.

This criterion LA50 is programmed into the model as a constant. To derive a criterion for a specific site, the site water chemistry data are input to the model. The model then uses an iterative approach to determine the dissolved copper concentration needed to achieve a Cu-biotic ligand concentration equal to the criterion LA50. This dissolved Cu concentration is, in effect, the FAV based on site water chemistry. The site-specific CMC is this predicted dissolved metal

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concentration (or criterion FAV) divided by two. The site-specific CCC is the CMC divided by the final acute-chronic ratio.

Next Steps. EPA has developed a draft criteria document that will undergo peer review. When EPA solicits scientific views from the public on the draft criterion, the model will be made available on the Office of Water web page at www.epa.gov/waterscience. Until the peer review is completed and a final copper criteria document is published by EPA, the procedures described here are draft and subject to change, and the criteria are not considered to be available for use. After completing the copper criteria update, EPA will consider incorporating the BLM into derivation procedures for other metal criteria, such as for silver, cadmium, and zinc. Although the BLM is currently appropriate for use in deriving an updated freshwater copper CMC, further development is required before using it to evaluate a saltwater copper CMC, a CCC, or a chronic value.

Alternative approaches may be considered to establish the database of input parameters for the acute toxicity studies, because the approach described in this document is labor intensive. Alternatives may include development of a few high-quality data sets that satisfy the minimum data requirements of the guidelines for a limited set of organisms or concentrating on developing data sets for known sensitive species. Estimating missing input parameters by relying on statistical techniques or Monte Carlo approaches may also be explored.

3.4.9.1.2. Implementation of BLM-Based Criteria

Draft guidance on how to implement BLM-based WQC for copper was released in late 2003 (EPA, 2003). Guidance on how to implement BLM-based WQC still needs to be developed. Because the water chemistry conditions that drive the BLM are time variable, it is difficult to determine what single criterion is appropriate for a given site. This is not unique to the BLM, as hardness-dependent metals criteria are also time-variable values. Multiple input parameters for the BLM complicate the calculation of site-specific criteria because of their combined effects on variability. EPA is currently addressing these limitations. At present, EPA expects that few sites have sufficient data for all the input parameters to enable adequate

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characterization of the inherent variation at a site. Therefore, the Agency is currently evaluating probabilistic techniques (Monte Carlo techniques) and statistical analyses to address this issue.

3.4.10. SEDIMENT TOXICITY

3.4.10.1 Metal Mixtures, AVS, and Sediment Bioavailability Issues

3.4.10.1.1. Rationale for Use of EqP Benchmarks.

Toxic pollutants in bottom sediments of the nation's lakes, rivers, wetlands, estuaries, and marine coastal waters create potential for continued environmental degradation even where water column concentrations comply with established human health and aquatic life WQC. In addition, contaminated sediments can be a significant pollutant source that may cause water quality degradation to persist even when other pollutant sources are stopped (U.S. EPA 1997a, b, c; Larsson, 1985, Salomons et al., 1987; Burgess and Scott, 1992). The scarcity of defensible sediment benchmarks and the single-chemical nature of those available make it difficult to (1) accurately assess the extent of the ecological risks of contaminated sediments, (2) establish pollution prevention strategies, and (3) identify, prioritize, and implement appropriate cleanup activities and source controls.

> No single approach has been found to be applicable for the derivation of sediment benchmarks in all situations. The **equilibrium partitioning** (EqP) approach has been applied to nonionic organic chemicals because it presented the greatest promise for generating defensible national chemical-specific sediment benchmarks applicable across a broad range of sediment types. However, sediment partitioning phases controlling interstitial water concentrations of metals are more complex, and are dependent upon **acid volatile sulfides** (AVS) in the sediments and dissolved organic matter (DOM) in the porewater. The term **EqP sediment benchmarks** (ESBs) refers to numerical concentrations for individual metals, or mixtures of metals, that are applicable across the range of sediment properties encountered in practice.

As a result of the need for guidance to assist agencies in making decisions concerning contaminated sediment problems and their prevention, a research team was established from EPA's Office of Science and Technology (OST) and ORD to review alternative approaches

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(Chapman, 1987). All of the approaches reviewed had both strengths and weaknesses, and no single approach was found to be applicable for the derivation of sediment benchmarks in all situations (U.S. EPA, 1989). The EqP approach was selected and first applied for nonionic organic chemicals because it presented the greatest promise for generating defensible national chemical-specific sediment benchmarks applicable across a broad range of sediment types. The term EqP sediment benchmarks (ESBs) refers to numerical concentrations for individual chemicals or mixtures of chemicals that are applicable across the range of sediments encountered in practice.

Because of their widespread release and persistent nature, metals such as cadmium, copper, lead, nickel, silver, and zinc are commonly elevated in aquatic sediments. These metals, in addition to nonionic organic chemicals, are of potential concern to aquatic environments. Thus, there have been various proposals for deriving sediment guidelines for protecting benthic communities using measurement of total sediment metals followed by comparison with background metal concentrations or, in some cases, an effects-based endpoint (Sullivan et al., 1985; Persaud et al., 1989; Long and Morgan, 1990; Ingersoll et al., 1996; MacDonald et al., 1996). An important limitation to these types of approaches is that the causal linkage between the measured concentration of metals and the observed toxicity cannot be established, in part because of the procedures used to derive correlative values and because values derived are based on total rather than bioavailable metal concentrations. That is, for any given total metal concentration, adverse toxicological effects may or may not occur, depending on the physicochemical characteristics of the sediment of concern (Tessier and Campbell, 1987; Luoma, 1989; Di Toro et al., 1990).

In developing ESBs for metals that causally link metals concentrations to biological effects and that apply across all sediments, it is essential that bioavailability be understood. Therefore, the EqP approach was selected as the technical basis for deriving ESBs for metals (U.S. EPA, 2002). Different studies have shown that although total (dry weight) metal concentrations in anaerobic sediments are not predictive of bioavailability, metal concentrations in interstitial water are correlated with observed biological effects (Swartz et al., 1985; Kemp and Swartz, 1986). However, unlike the situation for nonionic organic chemicals and organic carbon

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(see Di Toro et al., 1991), sediment partitioning phases controlling interstitial water concentrations of metals were not readily apparent. A key partitioning phase controlling cationic metal activity and metal-induced toxicity in the sediment-interstitial water system is AVS (Di Toro et al., 1990, 1992). AVS binds, on a molar basis, a number of cationic metals of environmental concern (cadmium, copper, lead, nickel, silver, and zinc), forming insoluble sulfide complexes with minimal biological availability.

3.4.10.1.1.2. *Application of the Approach*. The metals ESB accounts for bioavailability of metals in sediments and their potential for effects in the aquatic environment, thereby providing an ecologically relevant benchmark. Two equally applicable ESBs for metals, a solid phase and an interstitial water phase, are provided. The solid-phase AVS ESB is defined as:

$$\Sigma_i\ [SEM_i] \leq [AVS]$$

(The total molar concentration of SEM is less than or equal to the total molar concentration of AVS.)

Because cadmium, copper, lead, nickel, and zinc are divalent metals, 1 mol of each metal can bind with 1 mol of AVS. The molar concentrations of these metals are compared with AVS on a one-to-one basis. Silver, however, exists predominantly as a monovalent metal, so that silver monosulfide (Ag_2S) binds 2 mols of silver for each mol of AVS. Therefore, SEM Ag will represent the molar concentration of silver divided by two, [Ag]/2, which is compared with the molar AVS concentration.

The interstitial water-phase ESB is:

$$\Sigma[M_{i,d}]/\ [FCV_{i,d}] \leq 1$$

(The sum of the concentration of each individual metal dissolved in the interstitial water divided by the metal-specific final chronic value (FCV) of each individual metal based on dissolved metal is less than or equal to 1; note that at present EPA does not have an FCV for silver.)

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This latter value is termed an interstitial water benchmark unit (IWBU). A requirement of the IWBU approach is that the toxicities of interstitial water metal concentrations be additive. Importantly, both the solid-phase AVS ESB and the interstitial water ESB are no-effect guidelines; that is, they predict sediments that are acceptable for the protection of benthic organisms. These ESBs, when exceeded, do not unequivocally predict sediments that are unacceptable for the protection of benthic organisms. The solid-phase AVS guideline avoids the methodological difficulties of interstitial water sampling that may lead to an overestimate of exposure and provides information on the potential for additional metal binding. Because the AVS guideline does not include other metal-binding phases of sediments, the interstitial guideline is also proposed. The use of both the AVS and the interstitial water guidelines will improve estimates of risks of sediment-associated metals. For example, the absence of significant concentrations of metal in interstitial water in toxic sediments having SEM$\leq$AVS and in nontoxic sediments having SEM>AVS demonstrates that metals in these sediments are unavailable. The $(\Sigma SEM\text{-}AVS)/f_{OC}$ correction (see below) can be used to refine the prediction of sediment toxicity where protection of benthic organisms is acceptable, uncertain, or unacceptable.

AVS guideline. Results of calculations using chemical equilibrium models indicate that metals act in a competitive manner when binding to AVS. That is, the six metals will bind with AVS to form their respective sulfides in the order of their increasing solubility: silver, copper, lead, cadmium, zinc, and nickel. Therefore, they must be considered together. There cannot be a guideline just for nickel, for example, because all the other metals may be present as metal sulfides and therefore, to some extent, as AVSs. If these other metals are not measured as a mixture, then the $\sum$SEM will be misleadingly small, and it might appear that $\sum$[SEM]<[AVS] when in fact this would not be true if all the metals were considered together. It should be noted that EPA currently restricts this discussion to the six metals listed above; however, in situations where other sulfide-forming metals (e.g., mercury) are present at high concentrations, they also must be considered.

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The equilibrium model used to derive the ESB for a mixture of the metals is presented below (see Ankley et al., 1996, for details). If the molar sum of SEM for the six metals is less than or equal to the AVS, that is, if

$$\sum_i [SEM_i] \leq [AVS]$$

where:

$$\sum_i [SEM_i] = [SEM_{Cd}] + [SEM_{Cu}] + [SEM_{Pb}] + [SEM_{Ni}] + [SEM_{Zn}] + 1/2[SEM_{Ag}]$$

then the concentrations of the mixtures of metals in the sediment are acceptable for protection of benthic organisms from acute or chronic metal toxicity.

Interstitial water guideline. The application of the interstitial water guideline to multiple metals is complicated, not because of the chemical interactions of the metals in the sediment-interstitial water system (as is the case with the AVS guideline), but rather because of possible toxic interactions. Even if the individual concentrations do not exceed the WQC continuous concentration (CCC) of each metal, the metals could exert additive effects that might result in toxicity (Biesinger et al., 1986; Spehar and Fiandt, 1986; Enserink et al., 1991; Kraak et al., 1994). Therefore, in order to address this potential additivity, the interstitial water metal concentrations are converted to IWBUs. This conversion is done by dividing the individual metal interstitial water concentrations by their respective WQC FCVs and summing these values for all the metals. IWBUs are conceptually similar to toxic units (TUs); however, the term IWBU was adopted because it is derived using the FCV, which is intended to be a “no-effect” concentration (i.e., toxicity would not usually be expected at 1 IWBU).

For freshwater sediments, the FCVs are hardness dependent for all of the divalent metals under consideration, and thus need to be adjusted to the hardness of the interstitial water of the sediment being considered. Because there are no FCVs for silver in freshwater or saltwater, this approach is not applicable to sediments containing significant concentrations of silver (i.e., $\Sigma SEM > AVS$). Because silver has the smallest solubility product (see Table 2-2) and the greatest affinity for AVS, it would be the last metal to be released from the AVS or the first metal to bind

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with AVS. Therefore, it is unlikely that silver would occur in the interstitial water of any sediment with measurable AVS (Berry et al., 1996).

For the *i*th metal with a total dissolved concentration, [Mi,d], the IWBU is

$$\sum_i([M_{i,d}]/FCV_{i,d}) \leq 1$$

where:

$$\sum_i([M_{i,d}]/FCV_{i,d}) = \sum_i([M_{Cd,d}]/FCV_{Cd,d}) + \sum_i([M_{Cu,d}]/FCV_{Cu,d}) + \sum_i([M_{Pb,d}]/FCV_{Pb,d}) + \sum_i([M_{Ni,d}]/FCV_{Ni,d}) + \sum_i([M_{Zn,d}]/FCV_{Zn,d})$$

3.4.10.1.1.3. *Enhancements to the Metals ESB*. The AVS guideline is a "one-way" guideline; that is to say that if the guideline is not exceeded, the sediments should not be toxic due to the metals included in the guideline, but an exceedence of the guideline does not necessarily mean that the sediments will be toxic due to the presence of those metals. One way to reduce the uncertainty of a prediction of toxicity is to normalize for the fraction of organic carbon in the sediment and use $\sum$SEM-AVS)/f_{OC} for the solid-phase guideline. The use of this guideline is described in the metals ESB.

The metals ESB currently applies to only six metals: cadmium, copper, lead, nickel, silver, and zinc. However, AVS can also be used to predict the lack of toxicity in sediments due to chromium because the presence of AVS in sediments is indicative of reduced sediments. Chromium is present primarily in its reduced form (CrIII) in reduced sediments, and in this form it is much less toxic and bioavailable than the oxidized form of chromium (CrVI) (Berry et al., in prep.). The use of AVS in the prediction of the lack of chromium toxicity in sediments will be described in an addendum to the metals ESB.

3.4.10.1.1.3. *Level of Protection*. The metals ESB should be viewed as an approach, as opposed to a specific number. The ESB calculates a concentration in sediment that will be protective of a given toxicological endpoint using partitioning theory. However, the level of protection of the benchmark is variable, depending on which toxicological endpoints are selected. The FCVs from the metals WQC are used in the ESB as examples because they are familiar and provide a widely

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accepted level of protection. Other toxicological endpoints could be chosen, however, if a different level of protection was desired. For example, the water-only, chronic no-effect concentration for a threatened or endangered species might be used as the toxicological endpoint. EqP theory could then be used to calculate a sediment concentration that would be protective of that species.

3.4.10.1.1.4. ***Limitations.*** It should be emphasized that these benchmarks are intended to protect benthic organisms from the direct effects of these six metals in sediments that are permanently inundated with water, intertidal, or inundated periodically for durations sufficient to permit development of benthic assemblages. They do not apply to occasionally inundated soils containing terrestrial organisms. These benchmarks do not address the possibility of bioaccumulation and transfer to upper-trophic-level organisms or the synergistic, additive, or antagonistic effects of other substances.

Bioaccumulation. The data appear to suggest that for these sediments collected from freshwater and marine locations in the United States, direct toxicity caused by metals in sediments is expected to be extremely rare. Although this might be true, these data by themselves are inconclusive. Importantly, it would be inappropriate to use the data from the above studies to conclude that metals in sediments are not a problem. In all of the above studies, the sediments were collected in the summer, when the seasonal biogeochemical cycling of sulfur should produce the highest concentrations of iron monosulfide, which might make direct metal-associated toxicity less likely than in the winter/spring months. Accurate assessment of the extent of the direct ecological risks of metals in sediments requires that sediment monitoring occur in the months of minimum AVS concentration, typically, but not always, November to early May. These yet-to-be-conducted studies must monitor, at a minimum, SEM, AVS, f_{OC}, interstitial water metal, and toxicity.

Bioaccumulation of metals from sediments when SEM is less than AVS was not expected, based on EqP theory. However, there is a significant database that demonstrates that metals concentrations in benthic organisms increase when metals concentrations in sediments on a dry-weight basis increase (Ankley, 1996). This has caused considerable debate (Lee et al.,

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2000), because it suggests that metal bioavailability may be related to dry-weight metals concentrations, and if the increase in bioaccumulated metal is related to effects, then effects may be related to dry-weight metals concentrations. Most importantly, these studies, and all other AVS-related testing, have overwhelmingly demonstrated that toxic effects of metals are absent in sediments when SEM is less than AVSs, even when bioaccumulation is observed, and that toxicity is not related to dry-weight metals concentrations. This suggests that the bioaccumulated metals may not be toxicologically available or of sufficient concentration in the organism to cause effects. In addition, these metals do not biomagnify to higher trophic levels in aquatic ecosystems (Suedel et al., 1994). Therefore, an ESB based on the difference between the concentrations of SEM and AVS is appropriate for protecting benthic organisms from the direct effects of sediment-associated metals and not for protecting against metal bioaccumulation.

3.4.10.1.1.5. *Use and Implementation*. In practice, the sediment benchmarks for these six metals are not exceeded, and benthic organisms are sufficiently protected (defined in this case as the level of protection afforded by the WQC), if the sediment meets either one of the following benchmarks:

- The solid phase benchmark: $\sum_i[SEM_i] \leq [AVS]$; in other words, if metal, measured as SEM, does not exceed AVS; or

- The interstitial water benchmark: $\sum_i([M_{i,d}]/FCV_{i,d}) \leq 1$; in other words, if the sum of the contributions of all six metals in the interstitial water would not be expected to cause chronic effects at the level of protection afforded by the WQC.

If the AVS or interstitial water ESBs are exceeded, there is reason to believe that the sediment might be unacceptably contaminated by these metals. Further evaluation and testing would, therefore, be necessary to assess actual toxicity and its causal relationship to the metals of concern. If data on the sediment-specific SEM, AVS, and organic carbon concentrations are available, the uncertainty bounds for $(\sum SEM\text{-}AVS)/f_{OC}$ described in the metals ESB could be used to further classify sediments as those in which metals are not likely to cause toxicity, metal toxicity predictions are uncertain, or metal toxicity is likely. For sediments in which toxicity is

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likely or uncertain, acute and chronic tests with species that are sensitive to the metals suspected to be of concern, acute and chronic sediment toxicity identification evaluations (TIEs), in situ community assessments, and seasonal and spatial characterizations of the SEM, AVS, and interstitial water concentrations would be appropriate (Ankley et al., 1994).

3.4.11. BIOACCUMULATION FACTOR/BIOCONCENTRATION FACTOR[1]

3.4.11.1. Bioaccumulation

Bioaccumulation can be defined as the net accumulation of a metal in a tissue of interest or a whole organism that results from exposure. Metal bioaccumulation can apply to the entire organism, including both metal adsorbed to surfaces or absorbed by the organism or to specific tissue. It is usually expressed on a weight (dry or wet)- adjusted basis. The bioaccumulation of metals arises from all environmental sources, including air, water, solid phases (organic and inorganic phases in soil and sediment), and diet and also represents a steady-state balance of losses from tissues and the body.

The **bioconcentration factor (BCF)** is the ratio of metal concentration in an organism to metal concentration in water, at a steady state. Metal concentrations are usually expressed on a weight-adjusted, whole-organism basis, and waterborne metals are expressed as total metals. BCFs have been developed primarily with hydrophobic organic chemicals in aquatic systems, but they have been applied to organic chemicals and metals in various matrices. Strictly speaking, metal bioconcentration in sediment and soil systems is the net accumulation of a metal in or on an organism from pore water only. Hence, in sediment and soil the denominator for the ratio should comprise the pore water concentration of metal, not the total metal concentration in the sediment or soil. In the broadest context, the **bioaccumulation factor (BAF)** is the ratio of the metal concentration in an organism to that in the surrounding medium at steady state.

Although BAFs and BCFs are generally calculated in a similar manner, the interpretation is slightly different with metal accumulation in organisms arising from water only for BCFs and

[1]BAF (Adapted from Drexler et al., 2003)

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from both water and dietary sources for BAFs. For aquatic organisms, BAFs are generally derived from measurements in natural environments, and BCFs are more readily measured under laboratory conditions. Unless metal concentrations in pore water serve as the denominator for the ratio, soil and sediment BAFs are usually termed BSAFs. Concentrations are usually measured on a total-metal and weight-adjusted whole-organism (or tissue) basis.

Toxicological bioaccumulation is the fraction of the metal that bioaccumulates and is distributed to receptors at sites of toxic action. For metals, this would include reactions with target proteins or other receptors that result in toxicity but not interactions with metallothionein and other metal-binding ligands or incorporation into granules that make metals unavailable for interactions with target molecules. This fraction is more conceptual in nature but is difficult to measure in practicality; it is akin to the minimal effective dose measured in blood that is often used in medicine for assessing therapeutic effects. It could be conceptually defined as a toxicological bioaccumulation fraction or the ratio of total metal concentration in an organism to the metal concentration at the site(s) of toxic action.

3.4.11.1.1. Scientific Issues

The application of BAF/BCF models to predict inorganic metals accumulation in biota has several scientific shortfalls (Drexler et al, 2003):

- Metal partitioning between water and fish is not related to physicochemical parameters such as lipid or octanol solubility.

- Uptake of inorganic metals is a physiological process that occurs via a number of specific routes, most of which involve saturable transport kinetics.

- The degree of uptake and ultimate internal fate of metals is strongly influenced by ligand binding and receptor site competitive interactions that control metal availability and/or transfer processes at the level of the aquatic or sediment medium, the biological membranes, the vascular and intercellular transfer mechanisms, and the intracellular matrix.

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- Evolution has occurred in the presence of continuous exposure to background levels of metals, and as a result there are physiological mechanisms to provide homeostatic control.

- BCFs for metals can be highly variable and can be inversely correlated to exposure concentrations (McGeer et al., 2003, and as discussed above), which can make a representative single value BCF for a metal meaningless.

- The approach of using one simplified bioaccumulation model (BCF and BAF) and applying it to inorganic metals without consideration of the basic physical and chemical differences between organic and inorganic substances and is not supported by theoretical and empirical weight of evidence.

The existence of inverse relationships between BCF (BAF) and exposure concentrations for certain metal/species combinations has led to recommendations by some to abandon the current use of BCFs and BAFs for classifying metal hazards (Adams, 2000; Brix and Deforest, 2000). The Organization for Economic Co-operation and Development (OECD) has published guidance for classifying metals that are hazardous to aquatic environments (OECD, 2001). The hazard classification schemes presented in the guidance incorporate, among other parameters, evidence of bioaccumulation as a basis for hazard ranking. The guidance advises, however, that in situations in which there is an inverse relationship between BCF and external water concentration the bioconcentration data should be used with care.

3.4.11.1.2. Possible Alternatives to BAF/BCF

Some of the following approaches may help to better interpret BCF and BAF data for metals.

Subtracting "normal" accumulation. This involves separating the portion of metal that bioaccumulates from exposure under "normal" conditions from that portion that occurs as a result of exposure to elevated levels of metals (McGeer et al., 2003). The accumulation factor (ACF) applies the concept behind the added risk approach proposed in the EU risk assessment process, accounting for the additional bioaccumulation that results from the added exposure. The ACF value also accounts for the accumulation of essential metals required for physiological

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function. ACF values were dramatically lower than BCF values (illustrating the importance of normal bioaccumulation) for some metals, particularly essential metals.

Limitations. There was no link to the potential for toxic impact (7), and there was an inverse correlation with exposure concentration. Perhaps the most useful aspect of this measure is that it incorporates essential and normal metal bioaccumulation into considerations of overall bioaccumulation.

Calculating BCF and BAF values over a limited range of concentrations. Limiting the calculation of BAF and BCF values to concentrations that approximate the applicable water quality criterion has also been suggested as a method for reducing the uncertainty around BCF and BAF values in situations where concentration dependency is evident. This would account for bioaccumulation at an exposure level where concern over bioaccumulation might be expected. On a site-specific basis where toxicity thresholds and species are better characterized, this approach may have value in reducing uncertainty.

Limitations. This measure was evaluated, at least partially, for some metals (McGeer et al., 2003) and did not appear to reduce the variability associated with BCF and BAF measurements (Table 7). An additional issue for this approach is that WQC reflect some of the more sensitive organisms, whereas the BCF and BAF measurements are not necessarily from the same organisms and include data from biota that may not be near the threshold for chronic impacts. Therefore, as a modifier for broad-based application, this variation of the BCF/BAF methodology does not appear to explain variability

Evaluating slopes of BCF versus exposure concentration. Even though the inverse relationship between metal exposure and BCF/BAF values makes the application potentially problematic, the nature of the inverse relationship can be used to derive information on bioaccumulation processes. The slope of the BCF/BAF value to exposure relationship is directly related to the ability of biota to control bioaccumulation over a range of exposure concentrations.

Limitations. Although conceptual evaluation of the slope relationship may have the potential to discriminate between metals on the basis of bioaccumulation, in practice a number of issues are unaccounted for. As can be seen in Table 8, many metals are intermediate in terms of

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slopes. Furthermore, there are significant differences when data are broken down and grouped according to species as compared to total pooled data.

3.4.11.2. Bioaccumulation in Relation to Dietary Toxicity

Discriminating between metals that have the potential to cause effects via trophic transfer and metals that do not is another approach that might be useful in distinguishing between metals, based on bioaccumulation and impacts. Metals taken up and stored within a prey organism may not pose harm to the organism, and may, or may not. be bioavailable in other predator organisms that feed on the organism in which the metals are stored. Thus, while bioaccumulation of a metal in a given aquatic organism may not necessarily be toxic to the organism itself, the accumulated metal may serve as a source of exposure and toxicity to predator species.

For example, it has been demonstrated that lead that is bioaccumulated in mussels and stored by the mussels in a detoxified form poses a potential hazard to mammals that eat the mussels. Regoli and Orlando (1994) fed mice diets that contained mussels in which lead had bioaccumulated and was stored in detoxified forms. Elevated levels of lead were observed in the blood, kidneys, and livers of the mice. The authors concluded that lead that is bioaccumulated in mussels and stored in a detoxified form within the soft tissues of the mussels is not only bioavailable in mammals (including humans) that consume the mussels, but could also cause harm to the mammals (Regoli and Orlando, 1994).

However, in situations where trophic transfer is of concern, the fraction of metal in tissues that is bioavailable to aquatic and terrestrial consumers should be determined. Not all bioaccumulated metal poses a risk to predator species. This differs for specific predator-prey-metal combinations; such information is not universally available and may need to be developed for specific cases. In particular, the effects of food preparation (cooking) on metal bioavailability should be considered when assessing risks to human consumers. Available kinetic models for predicting metal bioaccumulation in aquatic food webs show the most promise when applied and calibrated on a site-specific basis, and efforts should continue to refine, evaluate, and apply these models where more intensive efforts are warranted.

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3.4.11.3. Alternatives to Tissue Burdens and Bioaccumulation

A key parameter that a bioaccumulation measure should be validated against is chronic toxicity. Because bioaccumulation criteria within the context of persistent, bioaccumulative, toxic substances are used as indicators of chronic toxicity (Franke et al., 1994; OECD, 2001), validation of linkages to chronic metal toxicity would provide confidence in their use and application.

3.4.12. SOIL TOXICITY

Variability of soil toxicity test results is due in part to the influence of soil properties on bioavailablity of metals (e.g., pH, organic matter, CEC). See Sections 3.1, 3.4.6, and 3.2, covering environmental chemistry bioavailability, terrestrial bioavailability, terrestrial exposure issues. Additionally, incorporation of sparingly soluble substances, such as many environmental forms of metals, into the soil matrix is difficult, and acclimation/adaptation of test organisms can further complicate test results. Use of soluble metal salts with the addition of organism to the test matrix immediately after mixing is not representative of most environmental situations, where aging and other physical/chemical processes affect metal speciation and uptake. Furthermore, testing of soil microbial function is particularly problematic because the test substance is added to soils with the microbial population already in place and that contain background amounts of metals.

3.4.12.1. Application

Modifications to standard toxicity bioassays for plants and soil organisms to account for properties of metals were discussed in an expert workshop and subsequently provided in Fairbrother et al. (2002). These include directions on type of soil matrices to use, mixing and aging of metals into the soil, and cautions about acclimation of test organisms. Future studies conducted specifically for development of toxicity endpoint values for metals can follow these suggested protocols and circumvent many of the past problems.

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However, there is a large body of literature on toxicity of metals to soil organisms that has already been developed, although often the objectives were to understand processes rather than to develop defensible toxicity thresholds. The challenge, therefore, lies in how to use these data, taking into account the test-to-test variability in soil chemistry parameters, and develop a technically defensible means of extrapolating toxicity responses across soil type—in other words, how to adjust the toxicity threshold values for bioavailability differences in test conditions. Ideally, the aBLM could be extended to terrestrial setting to account for differences in bioavailability due to environmental chemistry, particularly for plants and soft-bodied soil invertebrates. Studies have been initiated to develop what has been referred to as a *terrestrial BLM*, or tBLM. The conceptual approach to development of a tBLM is very much the same as for the variations of the BLMs that have been developed for aquatic settings (Allen, 2002). Although not currently developed to the point of being of practical use, experimental testing and model development programs are fully underway in the hope of providing a tool that will be of great practical utility in the relatively near future.

Another approach to addressing soil variability in soil toxicity tests is to normalize test results by dividing the LC50 by percent organic matter (van Gestal, 1992). This approach is based on observed correlations between the LC50 of copper to earthworms and soil organic matter content. Clay content was added by van Straalen (1993), who suggests normalizing no-observed-effect concentration data using the equation:

$$R = 15 + 0.6\,(L + H)$$

where:

R = background
L = clay content
H = organic matter content

Most recently, CEC has been shown to be the most important factor modifying zinc bioavailability in soils for both invertebrates and plants, and it will presumably show a similar relationship with other cationic metals (Smolders, 2003 presentation in DC; based on work by C.

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Janssen, Univ. Ghent). Therefore, effect responses in different soil types can be normalized on the basis of relative CEC. It must be remembered that CEC is a function, at least in part, of soil pH. Therefore, normalization is best done within similar pH ranges. However, comparison of field data with laboratory toxicity response information is best done through measuring metals in soil pore water from field assessments and comparing such data to spiked laboratory soils.

Preliminary studies suggest that consideration of aging may result in significant overestimates of effects from laboratory studies (Smolders, 2003 presentation in DC, based on work by C. Janssen, Univ. Ghent). Until such time as the data become available for metals of concern, the European community is reducing laboratory-derived toxicity values by a factor of 3 across all soil types to account for aging, except when assessing acute (short-term) risks of spills (Smolders, 2003 presentation in DC).

Because most soil properties are correlated to some degree, isolating individual soil parameters and relating them to soil biota toxicity is difficult. Treating the soil like a black box and using sequential extraction techniques has been useful in determining what fraction of the metals are in a labile form (Kabata-Pendias and Pendis, 2000). However, some scientists have questioned the usefulness of this process (Morgan and Morgan, 1988).

3.4.12.2. Limitations

Only two methods have been proposed in the literature for normalizing toxicity data across soils to account for differences in bioavailability: adjusting of endpoint values by percent organic matter in the soil or as a function of organic matter plus clay content. Both methods fail to incorporate either pH or cationic exchange capacity, both of which are of critical importance in determining bioavailability. Aging of metals in soils also is not included in these approaches. Furthermore, the data sets used to generate the relationships were not sufficiently robust to make generalizations possible across all soils and all organisms. The development of a tBLM shows promise as a method that will overcome these limitations; however, it likely will not be completed for at least 2 years after the publication of this Framework.

The use of a tissue residue approach has been suggested as another method to address soil chemistry and metal toxicity issues, suggesting that a metal concentration must reach a threshold value in the organism or at the target site before effects begin to occur (McCarthy and Mackay,

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1993; Lanno and McCarty, 1997). For essential elements in plants, deficiency/sufficiency concentrations in foliage have been developed. However, the relationship between toxicity and tissue residues is complex and varies depending on tissue type (roots vs. shoots), plant species, and metal. Little information is available for soil invertebrates, so relationships between tissue concentration and toxic response cannot yet be developed. Therefore, this approach, although conceptually sound, requires significant research before critical tissue levels can be established.

For plants, a large proportion of the toxicity literature was developed in support of understanding potential toxicity and metal uptake from biosolids. It is difficult to determine single-species, single-metal thresholds from this database for several reasons. First, biosolids tend to contain a mixture of metals, so any response observed cannot be attributed to a single metal and must account for potential antagonism or synergies that might occur (see Section 3.x.x. Mixtures). Second, biosolids are, by their nature, high in organic matter, which significantly affects bioavailability of the metals. Until a robust method is developed to adjust toxicity endpoints for the influence of organic matter (and other bioavailability factors), it will remain difficult to apply such results to unamended soils. The additional organic matter also provides excess nutrients to the plants, which further confounds possible metal effects. The guidance provided for development of EcoSSLs values (U.S. EPA, 2003) provides further guidance for applicability of literature studies to plant or soil invertebrate toxicity threshold determinations.

3.4.13. FOOD CHAIN (WILDLIFE) TOXICITY

Toxicity in wildlife from metals exposures is generally poorly understood and is rarely quantified in field settings. A few notable exceptions are those mechanisms described in avian waterfowl exposure to selenium (U.S. DOI, 1998; Adams et al., 2003), exposure of waterfowl to lead-contaminated sediments (Beyer et al., 1998; Blus et al., 1991; Henny et al., 2000), and white-tailed ptarmigan exposure to cadmium in vegetation (Larison et.al. 2000). Most metals express multiorgan toxicity, resulting in a general decrease in overall vigor, as opposed to well-defined mechanisms of action documented from organic xenobiotics such as pesticides. Typically, toxicological data used to assess the risk of many metals to wildlife are derived from laboratory species such as rats or mice or domestic livestock species (e.g., cattle, chickens)

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exposed to soluble metal salts. Extrapolating the results of such tests to evaluate toxicity to wildlife is necessary because of the paucity of data on the toxicity of metals to these receptors. However, extrapolation of results should be approached with caution due to the large amount of uncertainty that could be introduced into the risk assessment process (Suter, 1993).

Laboratory and domestic species may be more or less sensitive to chemicals than is the selected receptor. Toxicological responses among species vary because of many physiological factors that influence the toxicokinetics (absorption, distribution, and elimination) and toxicodynamics (relative potency) of metals after exposure has occured. For example, differences in gut physiology, renal excretion rates, and egg production influence the toxicokinetics of the metal. The ability of some species to more rapidly produce protective proteins such as metallothionein after exposure to metals are toxicodymamic features leading to interspecific extrapolation uncertainty. For example, mammal studies should not be extrapolated to birds, and extrapolation of data from rats (simple, monogastric digestive physiology) to ruminants introduces more uncertainty than does extrapolation from rats to canids, and so on. In the case of metals, where some species are able to regulate or store metals residues in their tissues without experiencing toxic effects (i.e., biota specific detoxification), extrapolations between species used to assess bioaccumulation and toxicity can be especially problematic.

3.4.13.1. Application

Methods for extrapolating metal effects data among species are not unique to metals risk assessment, with the exception of understanding different requirements for essential elements. Some of the methods for extrapolating effects data among species include body weight normalization (Sample et al.,1996), distribution-based approaches (Van Straalen, 2001), or the use of uncertainty factors (e.g., Calabrese and Baldwin, 1994). All of these approaches suffer from a lack of an underlying physiological basis quantifying toxicokinetic and toxicodynamic responses among species. A review of potential extrapolation methodologies can be found in U.S. EPA (2003)

Currently, the best sources of information on metal toxicity thresholds are NRC (1980; 1994), McDowell (2003), and the documentation supporting development of EcoSSLs values (U.S. EPA, 2003). The EcoSSL document also includes a general approach for screening studies

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for acceptability for use in derivation of toxicity thresholds for risk assessments that can be used for deriving site-specific TRVs for the most applicable endpoints. These endpoints should then be extrapolated to species with similar physiology, particularly of the digestive system, due to the predominance of the dietary exposure pathway (e.g., cow data can be applied to wild bovids such as bison and possibly to other ruminants such as deer or elk). Uncertainty factors can be carefully applied if there is concern for extrapolation of data to species in a different taxonomic category (e.g., genus, family, class). General summaries for some metals are available in Bayer et al. (1996) and Fairbrother et al. (1996).

3.4.13.2. Limitations

Information on toxicity of metals to wildlife under field conditions is severely limited, focusing on only a few species and a few metals. Deriving TRVs for metals in wildlife is problematic because the administered form of metal is typically not found in most applied settings. For example, lead has one of the largest databases for laboratory exposures but has been limited by the form of the metal studied. Until recently, almost all field studies were conducted in support of toxic effects of lead shot (i.e., pure elemental lead), whereas almost all laboratory studies have administered lead to test subjects as lead acetate. These extreme forms of RBA of lead make extrapolations to dietary exposures difficult for this substance. The best approach in this case is the use of critical tissue residues, because liver lead levels indicative of lead poisoning are well established (Beyer et al., 1996). Selenium is another example where tissue-based toxicity thresholds (in this case, in the avian egg) may be most appropriate (e.g., Adams et al., 2003).

Cross-species extrapolations must be conducted with some knowledge of animal physiology and specific responses to metals. Digestive physiology is the most important distinction, because most metal exposures in wildlife are by the dietary route. However, other specific organismal responses need to be understood as well. For example, sheep are much more sensitive to copper than are other ruminants because of the particular nature of their gut flora (NRC, 1980). Therefore, extrapolation of sheep data to other ruminants would be highly overconservative. On the other hand, pigs are extremely tolerant to copper, possibly due to low

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gut uptake rates (NRC, 1980), so extrapolations of such data to other monogastric animals would not be protective.

Interactions of metals (see Section 3.3. Human Health) also must be taken into account when analyzing metal toxicity data for wildlife. As noted above, values that may be protective for a particular metal within a certain animal may not be so if other metals are present or deficient (or vice versa). Therefore, dietary studies must be examined to understand the presence of other metals and to ascertain the sufficiency of essential elements. Application of single-metal thresholds to field situations, whether in a site-specific context or on a national scale, must make provision for adjustment to account for interactive effects.

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4.0. ASSESSMENT RECOMMENDATIONS AND METHOD APPLICATIONS FOR METALS

Metals risk assessments differ from similar assessments for organic substances because of the unique physical, chemical, and biological properties of metals. These were reviewed in depth in Section 3, including the limitations imposed on the risk assessment either by lack of knowledge or incomplete data. This section summarize the information from Section 3 into the primary attributes that must be kept in mind when conducting assessments for environmental or human health risks of metals. The recommendations are made not as a prescriptive guide, but to foster the consistent application of methods and data to metals risk assessment in consideration of the unique properties of metals. Sections 4.1 to 4.3, addressing aquatic, terrestrial, human health, and atmospheric assessments, present recommendations under the various topics discussed in Section 3 to assist assessors in conducting risk assessments on metals. Section 5 reviews research needs and the progress and plans of the Unit World Model, an innovative, and integrated proposed new approach for metals assessments.

Three Major Categories of Metals Assessments

1.) Ranking and Categorization

Ranking or categorization of chemicals based on their potential to cause risk.

2.) National Assessments

National level assessments are typically performed when the Agency is setting media standards or guidelines for chemicals

3.) Site-Specific Assessments

Site-specific assessments are conducted to inform a decision concerning a particular

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For the purposes of this report (see Section 1.5), EPA has defined three general categories of assessments: 1) National Ranking and Categorization, 2) National Assessments, and 3) Site-Specific Assessments. Each of these types of assessment can vary in their level of detail from simple screening analyses to highly complex studies. To further delineate the application of the recommendations for these models and methods, tables at the end of each subsection present a qualitative guide for the type of analysis that is most appropriate for a particular assessment level.

4.1. METALS ASSESSMENT TOOLS FOR AQUATIC ECOSYSTEMS

This sections presents recommendations for assessing exposure and effects of metals in aquatic systems. Particular methods and models described in the recommendations are discussed in more detail in section 3, the metal issue papers, and referenced citations.

4.1.1. Fate & Transport

Predictions of fate and transport of metals in aquatic systems is best accomplished through the use of integrated models, rather than sophisticated stand-along hydrodynamic or sediment transport models. While these more sophisticated models are useful for examining and developing input parameters for the integrated models, they do not work well with each other, thus introducing large uncertainties when assessing the system as a whole. The exception are chemical speciation models that are vital both for input to fate and transport models and for predictions of bioavailability. A list of aquatic system fate and transport models is provided in Section. 3.2.

Water quality analyses often require probabilistic results, as the Water Quality Criteria specify not-to-exceed concentrations for a once in 3-year return period. Steady-state models cannot evaluate a return period for exceedences. When using these models, a Monte Carlo analysis can be conducted to generate a large number of model inputs and subsequent solutions, which can then be analyzed statistically to characterize the exceedence probability. Time-

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variable models that generate long-term simulations (e.g., 20 years) can also be statistically analyzed to evaluate the frequency of exceedences.

The single most important parameter in modeling the transport and fate of metals in aquatic systems is the equilibrium partition coefficient value(s) used to characterize the distribution of metals between water (dissolved) and particulates (sorbed). The magnitude of the partition coefficient is described in proportion to the amount of dissolved organic matter (generally quantified by the amount of dissolved organic carbon). In modeling metal movements, the equilibrium partition coefficient value is proportional to total dissolved metal (free ionic forms + amount complexed with dissolved organic carbon). This reflects transfer of the sorbed metal between water and sediment compartments in proportion to amount of settling and reexchange of particulates, as well as the flux of metals into sediment porewater. Partitioning reactions also determine the amount of bioavailable metal. However, assuming equilibrium conditions is a known over simplification of most systems, and results in considerable uncertainty in estimates of dynamic systems or situations where metals are either continuously being discharged or immediately following a pulse exposure.

***Recommendations*:**

- Assessors need to keep in mind that all modeling exercises are limited by the assumptions, associated uncertainties, validity of the model framework, the accuracy of input parameters, and the experience of the analyst.
- Typically, complex time-variable models are appropriate only for more complex situation in higher tiered analyses.
- It is recommended that the use of partition coefficients consider the strengths and limitations discussed in Section 3.1.
- Predictions of fate and transport of metals in aquatic systems is best accomplished through the use of integrated models, rather than sophisticated stand-along hydrodynamic or sediment transport models.

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- Consideration of metal speciation is vital to accurate predictions of metal partitioning and modeling of fate and transport in water and sediment.

4.1.2. Exposure Pathways

4.1.2.1 Water Column

Potential exposure routes for aquatic species include inhalation/respiration, dermal absorption, and dietary (from either food or incidental sediment ingestion). Due to the diversity of aquatic organisms, the extent to which a metal is taken up by any one of these exposure routes is difficult to define for all relevant routes. The respiration/inhalation route is a particular challenge in aquatic exposure assessments due to differing types of respiratory organs, the dynamic nature of the respiratory process in water, and the intimate contact between a receptor and metals dissolved in waters (Newman et al. 2003). General statements on metal exposure by ingestion is complicated by the diversity of feeding modes and digestive systems of candidate receptors, as well as the possibility of exposure after passage through a food web (Newman, et al., 2003).

The combination of the Free Ion Model (FIAM) and the Biological Ligand Model (see Section 3.4. Ecological Effects, Aquatic) indicates that a dissolved metal ion's bioactivity is a function of its complexation with dissolved ligands (which determines how much free ion will be available for binding with biological ligands), and the affinity and stability of the metal complexes with the biological ligands. Further complexation of metals takes place within the cells of the respiratory organ, with the remaining free metal available for binding to transport macromolecules for delivery to the organism's circulatory system; this results in the true delivered dose. These metal exposure models have been effectively linked to water quality criteria (see Sec 3.4 ecological effects).

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***Recommendations*:**

- With deference to the discussion above, the binding of metals to the gill surface is the primary route of exposure for most water column organisms, at least for short duration exposures.
- Currently, no standard approaches exist for the application of dietary exposure estimates in water quality assessments (Schlekat et al., 2001).

4.1.2.2. Sediments

There are two major approaches for assessing sediment exposure and subsequent effects: the equilibrium partitioning approach (EqP) and simultaneous extractable metals - acid volatile sulfides (SEM-AVS). Other approaches include sequential extractions with different media (water, weak acids, strong acids) or normalization to total iron or organic carbon. Each has its strengths and limitations. Detailed discussions are provided in Paquin et al. (2003) and Newman et al. (2003), with additional information and recommendations in Section 3.4 Ecological Effects, Aquatic. Recommendations are in the sediment effect discussion in this section

4.1.2.3. Trophic Transfer and Biomagnification

Trophic transfer and biomagnification are terms used to describe the transfer of a substance from a prey species to a predator species. Biomagnification typically describes circumstances when chemical concentrations increase across multiple trophic levels, a situation which for the most part does not occur for metals (McGeer et al., 2003). The biomagnification of inorganic metals in aquatic organisms is rare (Drexler et al., 2003).

Trophic transfer refers to substances transferred from one trophic level to the next as in a prey being consumed by a predator. Trophic transfer is an important issue for metals. primarily for phytoplankton that bioaccumulate some metals, making them available for trophic transfer (Drexler et al. 2003). Also, organisms that accumulate metals from sediments, if consumed by aquatic animals, can translocate sediment-bound metals into an aquatic food web. However, biodilution can also occur for metals as Chen and Folt (2000) observed for As and Pb. A prey

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organism with a high concentration of a particular trace metal represents a potential opportunity for the trophic transfer of higher amounts of metals to a predator at the next trophic level. Metals are often detoxified and stored in the prey species and the bioavailability of those stored metals is significant for the potential assimilation of that metal by the predator (Wang and Fisher, 1999). Metals taken up and stored within a prey organism may not pose harm to the organism itself, but may be bioavailable in other predator organisms that feed on the organism in which the metals are stored. Thus, while bioaccumulation of a metal in a give aquatic organism may not necessarily be toxic to the organism itself, the accumulated metal may serve as a source of exposure and toxicity to predator species. Trophic transfer coefficients above one can occur when the assimilation efficiency of the metal is very high, and the corresponding metal excretion rate is very low (Wang, 2002; Reinfelder et al., 1998). A generalization that may be useful to group metals with a greater potential for trophic transfer is that Class B and intermediate metals have greater binding potential to algal components than do Class A metals (Reinfelder and Fisher, 1991). Therefore, Class B metals are more likely to transfer to the next trophic level in the food web and result in higher exposures of aquatic organisms

***Recommendations*:**

- Because the biomagnification of inorganic metals in aquatic organisms is rare, its use in assessments is of limited value.
- Consideration of metal trophic transfer is primarily important for phytoplankton
- Assessors may need to consider trophic dilution for other aquatic species.

4.1.2.4. <u>BAF/BCF</u>

Bioaccumulation can be defined as the net accumulation of a metal in a tissue of interest or a whole organism that results from exposure. A bioconcentration factor (BCF) is the ratio of metal concentration in an organism to metal concentration in water, at a steady state and a bioaccumulation factor (BAF) is the ratio of the metal concentration in an organism to that in the

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surrounding medium, at steady state. These topics are further discussed in Section 2.2, Drexler et al. 2003, and other publications (McGeer et al., 2003).

Drexler et al.(2003) offered several appropriate suggestions on the BAF/BCF approach. They included discussions on its limitations, when BCF/BAF is and is not applicable, concentration dependency, and uncertainty issues (see Section 3.4). Additional guidance on modification to BCF/BAF and alternative techniques was also recommended. Further research is needed in this area to address these issues.

***Recommendations*:**

- The current science does not support the use of a single BAF/BCF as a reliable indicator of acute or chronic hazard for metal substances for use in national ranking and categorization.
- The current science does not support the use of a single BAF/BCF in general as a reliable indicator of acute or chronic hazard for metal substances for use in national level assessments. However, in some national level assessments, where data are available to relate accumulated metal concentrations to specific toxicological levels of concern for particular species, quantification of BAF/BCF and associated uncertainty for inorganic metals may be possible provided it is based on consideration of organism-specific issues, such as essentiality, metal regulation, detoxification and storage, background accumulation, and inverse relationships between BAF/BCF and exposure concentration.
- For site-specific assessments, the BAF/BCF process is the most applicable with values calculated over a limited range of concentrations and using a data base of site specific toxicity thresholds and species.

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4.1.3 Toxicity Assessment

4.1.3.1. Ambient Water Quality Criteria (AWQC)

Ambient water quality criteria (AWQC) are developed to support the Clean Water Act and since the 1980s aquatic life criteria for several cationic metals have been expressed as a function of water hardness to address the relationship of certain cations on toxicity. EPA's Office of Water (OW) recognized that water hardness adjustments did not account for other important ions and ligands that can alter metals bioavailability and toxicity at specific sites and they developed an approach to address this issue, the Water Effect Ratio (WER). WER is an empirical approach to make site-specific bioavailability adjustments to criteria (U.S. EPA, 1994). This approach relies on comparing toxicity measurements made in site water to those made in laboratory water to derive a WER. The WER is then used to adjust the national criterion to reflect site-specific bioavailability.

To address other factors that modifying metal bioavailability such as pH and competing ligands, OW has recently been working with the scientific community to develop a mechanistic-based approach for addressing metals bioavailability using the Biotic Ligand Model or BLM (U.S. EPA, 2000g; DiToro et al., 2000, 2001; Santore et al., 2001, Paquin et al., 2002). This model, which is described in further detail in Section 3.4, predicts acute toxicity to aquatic organisms based on 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 with the release of a draft acute BLM for Copper (EPA, 2003), which incorporates BLM directly into the national copper aquatic life criterion. The BLM is also being developed for use with other metals including silver. Conceptually, the BLM is appealing because metals criteria could be implemented to account for predicted periods of enhanced bioavailability at a site which may not be captured by purely empirical methods such as the WER. Research challenges include filed validation issues and the development of chronic BLM approaches and values.

The applicability of the BLM is being extended to chronic toxicity through the use of the Ion Balance Model (IBM) of Paquin et al. (2002a, 2002b, 2002c). While the approach, which

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was initially applied to silver, may ultimately provide a way to predict effects due to metals over varying exposure durations, further development and testing is required.

***Recommendations*:**

- WER is an empirical approach that may be used to make site-specific bioavailability adjustments to water quality criteria (U.S. EPA, 1994).
- the BLM is a tool for predicting acute toxicity accounting for individual water quality parameters and is an approach that offers flexibility to be adapted to specific systems or site specific locations.

4.1.3.2. Sediment Effects

Various tools to relate sediment metal concentrations to effects on aquatic biota have been developed (NRC, 2003). Due to the complexity of sediment physical and chemical parameters, metal chemistry, and biological uptake and response, all methods have some limitations and/or areas of scientific debate. While mechanistic understandings of the toxicity of metal contaminated sediments are needed (Newman et al., 2003), the complexities of metal-sediment interactions make this difficult to achieve. EPA (2002) published a report on the application of solid-phase AVS equilibrium partitioning sediment benchmarks (ESBs) and interstitial water ESB as no-effect guidelines; that is, they predict sediments that are acceptable for the protection of benthic organisms. Equilibrium partitioning sediment benchmarks (ESBs) refers to numerical concentrations for individual chemicals or mixtures of chemicals that are applicable across the range of sediments encountered in practice. Understanding metal bioavailability is essential in developing ESBs that causally link sediment metal concentrations to biological effects. Details of the AVS-SEM method are discussed in Section 3.4 and the issue papers. The method has been applied to predict toxicity of metals in sediment for Class B or borderline Class B metals. An ESB based on the difference between the concentrations of SEM and AVS is appropriate for protecting benthic organisms from the direct effects of sediment-associated metals, and not for estimating metal bioaccumulation. The solid-phase

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AVS-SEM approach avoids the methodological difficulties of interstitial water sampling that may lead to an overestimate of metal exposure. Limitations concerning the AVS-SEM approach are discussed in Section 3.4 and in Chapman et al. (2003).

***Recommendations*:**

- The AVS-SEM approach is most applicable to organisms whose primary exposure is through interstitial water, and does not account for dietary exposure and associated incidental sediment ingestion.
- As a screening-level tool, the toxicity of anoxic sediments is low when AVS is in excess (AVS > SEM) which implies sufficient capacity of AVS to bind essentially all free metal.
- Because of its reliance on the chemistry of bulk anoxic sediment, the AVS-SEM method may not be appropriate for benthic organisms living in oxygenated burrows.
- Additional site specific testing for sediments in which toxicity is likely or uncertain may be required

4.1.3.3. Interstitial Water Guidance

The interstitial water phase ESB and an interstitial water benchmarks unit (IWBU) approach is discussed in Section 3.4, ecological effects, and is an additive approach to address the toxicities of interstitial water metal concentrations. The technique uses WQC and final chronic values (FVC) to determine no effect concentrations for six metals. The technique sums the ratios of metal concentrations in interstitial water over the appropriate FCV.

However, because the AVS-SEM method does not include other metal-binding phases of sediments, the interstitial guideline should be used with the AVS-SEM methods to substantially improve estimates of risks of sediment-associated metals. ESBs currently apply to only six metals: cadmium, copper, lead, nickel, silver, and zinc. In practice, the sediment benchmarks for these six metals are not exceeded, and benthic organisms are sufficiently protected (defined in

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this case as the level of protection afforded by the water quality criteria), if the sediment meets either one of the following benchmarks:

- AVS-SEM benchmark – The metals measured as simultaneously extracted metal, do not exceed acid-volatile sulfide;
- Interstitial water benchmark – The sum of the contributions of all six metals in the interstitial water would not be expected to cause chronic effects at the level of protection afforded by the water quality criteria.

***Recommendations*:**

- The solid-phase AVS ESB and interstitial water ESB used together are useful are useful as no-effect guidelines that predict sediments that are acceptable for the protection of benthic organisms. These ESBs, when exceeded, do not unequivocally predict sediments that are unacceptable for the protection of benthic organisms.

4.1.3.4. Oxic Sediments

For oxic sediments several tools have been developed to relate metal lability/availability in sediments to toxicity. Tessier et al. (1984, 1989, 1993) compiled pH dependent partition coefficients of metals that were determined from field studies of freshwater sediments. The partition coefficients are generally linear over a range of pore water pH values. Chemical, acid, and biomimetic extraction methods have been used (Newmanet al., 2003; NRC, 2003), however, no consensus exists yet about their best use for different types of metals or metalloids.

4.1.3.5. Metals Mixtures

Currently, there are no realistic means to rank mixtures of metals or individual metals within mixtures. National criteria for mixtures are possible for acute effects, but not for chronic effects. For acute effects, two methods were discussed in Section 3.4: the Concentration Addition Model, where all metals in a mixture are added together to predict toxicity, with

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differing potencies taken into account by converting chemical concentrations to an equitoxic dose using either toxic units (TUs) or toxicity equivalence factors (TEFs) (for aquatic organisms, this can be accomplished through the application of the BLM). These calculations convert all metals to a single metal concentration. Alternatively, the QICAR Effects Addition approach may be used to predict the potential for binary interactions of metals with joint independent action. The deviation from independent joint action can be predicted from the degree of similarity in binding tendencies for the paired metals. However, both of these approaches still encompass significant uncertainty. In a recent review of 191 cases in aquatic systems (Norwood et al., 2003), 70% were additive or less than additive. Also, the Concentration Addition approach is only recommended only for application to mixtures with less than six components.

***Recommendations*:**

- For acute exposures, toxicity of cationic metals is additive provided bioavailability adjustments are made (e.g., using the BLM approach).
- Methods to assess the chronic effects of metal mixtures are limited. More method development is needed.

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Table 22 presents a qualitative guide on the appropriate use of the recommendations for a particular assessment level. While it is recognized that within an assessment level the types of assessment can vary in detail from simple screening analyses to highly complex studies, the general trend in the application of metal specific methods will increase from ranking to national criteria to site specific assessments.

Table 22. Application of Aquatic Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Fate & Transport	Steady-state models are sufficient for the situations where simplification is acceptable.	Steady-state models are sufficient for the situations where simplification is acceptable. Complex time-variable models should be used for more complex situation in higher tiered analyses.	Steady-state models are sufficient for screening. Complex time-variable models should be used for more complex situation in higher tiered analyses.
Exposure Pathways	Not applicable when ranking and categorization are based on hazard only.	Complex issue to generalize; Binding of metals to the gill surface is the primary route of exposure for most water column animals.	Binding of metals to the gill surface is the primary route of exposure for most water column animals.
Trophic Transfer and Biomagnification	Biomagnification in aquatic organisms is rare.	Biomagnification in aquatic organisms is rare. Trophic transfer is an important issue particularly for phytoplankton; Biodilution can occur.	Site specific data will indicate if trophic transfer is of concern.

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Table 25. Application of Aquatic Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
BAF/BCF	The current science does not support the use of a single BAF/BCF as a reliable indicator of acute or chronic hazard for metal substances.	The current science does not support the use of a single BAF/BCF in general as a reliable indicator of acute or chronic hazard for metal substances. However, in some national level assessments, where data are available to relate accumulated metal concentrations to specific toxicological levels of concern for particular species, quantification of BAF/BCF and associated uncertainty for inorganic metals may be possible provided it is based on consideration of organism-specific issues, such as essentiality, metal regulation, detoxification and storage, background accumulation, and inverse relationships between BAF/BCF and exposure concentration.	BAF/BCF is most applicable with values calculated over a limited range of concentrations and using a data base of site specific toxicity thresholds and species.

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Table 25. Application of Aquatic Tools to Metals Assessment Levels

	Tools	Ranking/Categorization	National	Site Specific
1	Ecological Effects	AWQC could be used in these activities.	The AWQC and the draft BLM approaches offer national criteria that offer flexibility to be adapted to specific systems or site specific locations. Unit World Model (Section 5.3.6) when developed will likely expand applicability.	The AWQC and the draft BLM approaches offer national criteria that offer flexibility to be adapted to specific systems or site specific locations. WER adjusts AWQC to specific aquatic sites. Direct toxicity testing can be used to supplement BLM predictions in site specific assessment.
2	Sediments	Methods not applicable to ranking.	With limitations acknowledged, ESBs offer a protective approach. In addition, AVS-SEM can be used as a national criterion.	AVS-SEM and interstitial methods provide screening for no effects. Site specific testing for definitive results. Toxicity testing can be used for site-specific assessment.

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Table 25. Application of Aquatic Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
oxic sediment	Methods not applicable to ranking.	Various chemical extraction methods are available; All have faults. Assessing metals in interstitial water is applicable to oxic sediments and can be applied as a national approach, as well as site specific.	Various chemical extraction methods are available; All have faults. Assessing metals in interstitial water is applicable to oxic sediments and can be applied as a national approach, as well as site specific.
Mixtures	Assume additivity (adjusted for bioavailability) for acute exposures, if modes of action are known to be similar.	Assume additivity (adjusted for bioavailability) for acute exposures, if modes of action are known to be similar. Toxicity testing can be used for verification or for assessing chronic (dietary) effects of mixtures.	Assume additivity (adjusted for bioavailability) for acute exposures and if modes of action are known to be similar. Toxicity testing can be used for verification or for assessing chronic (dietary) effects of mixtures.

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4.2. METALS ASSESSMENT TOOLS FOR TERRESTRIAL ECOSYSTEMS

As with any chemical, toxicity of metals generally are estimated by the use of standard laboratory bioassays that are conducted in a manner similar to tests performed with organic substances. However, the response of organisms to metals is complicated by several factors that need not be considered for most organic substances. These include the natural background concentrations of the metals (including, but not limited to the metal of interest) in either the test media or the site of concern, the acclimation of test animals to the culture conditions, whether or not the metal is an essential micronutrient, potential interaction of the various metals, and the bioavailability of the metal. Recommended methods used to account for the influences of each of these factors that modify toxicity are presented here.

4.2.1. Fate & Transport

4.2.1.1. Soil Mobility

Primary processes governing the environmental fate and transport of metals in the subsurface are advection, dispersion, matrix diffusion, and retardation (U.S. EPA, 1994). Advection and dispersion are functions of the system rather than of the contaminant, so are not specific to metals. Matrix diffusion, which is a function of the contaminant, is relatively unimportant and is omitted in most soil transport models. Retardation is contaminant and site specific. Because of this complexity, and the interactions between metals and environmental factors, single partition or distribution coefficients (K_d) are used as default approaches.

Recommendations:

- Models using K_d have significant inaccuracies for metals, and the application of single partition coefficient values for individual metals should be limited to regional and national scale studies where accuracy is not required and bounding or representative values are adequate.
- Assume linearity of log K_d with pH as a default approach for national type assessments

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- Obtain metal K_d information from U.S. EPA, 1998 and 1999b.
- If fluid flow in porous soil is isotropic and adsorption is fast, reversible, and linear use the diffuse layer (DL) model (also called the generalized two-layer model, or GTLM) in MINTEQA2 to predict adsorption and precipitation behavior as a function of pH.
- PHREEQC, which has the DL metal adsorption model, can be used with HST3D, a groundwater flow and transport model and CHMTRNS also can be used to model metal transport through porous media.

4.2.1.2. Transformation in Soils

Methylation and demethylation of organic mercury compounds in soils are mediated by the same types of abiotic and microbial processes that occur in aquatic systems. Because soils are primarily oxygenated systems, particularly in the root zone, conditions favorable to sulfide formation and bacterial methylation occur infrequently. With the exception of peat bogs and similar anoxic, highly saturated soils, methylation generally occurs only at very low rates in soils. Plants also can transform metals and metalloids taken up from the soil. The most notable example is selenium. Soluble inorganic oxanions of selenium are readily taken up by plants and converted to organoselenium compounds such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide.

Recommendations:

- Assume mercury in soils, plants, and soil invertebrates can be assumed to be inorganic mercury
- Selenium in soils should be assumed to be in the inorganic form
- Selenium in plants and soil invertebrates should be considered as an organic compound for food chain analysis.
- Volatilization of all metalloids (mercury, selenium, arsenic) and organometallics should be considered when conducting detailed site-specific fate and transport models.

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4.2.2. Exposure Assessment

Terrestrial wildlife, plants, and invertebrates accumulate metals from direct contact with soil or sediment, from ingestion of contaminated food (plants or other animals), and from incidental soil or sediment ingestion. Pathways of exposure include movement from soils through the food web and, to a lesser extent, air deposition either into soils or directly onto terrestrial receptors (e.g., plants). Because of significant differences in exposure patterns, it is convenient to discuss methods by receptor group (invertebrates, plants, wildlife) rather than by pathways or environmental compartments, with the exception of contribution of natural background to total exposure which is applicable to all organisms.

4.2.2.1. Background

Detailed guidance on estimating background concentrations for site-specific assessments is provided in U.S. EPA 2000, 2002b, and 2002c. State-wide average background soil concentrations are available in the U.S. EPA EcoSSLs document (EPA, 2003). Additional information on concentration of metals in soils at smaller spatial resolutions is in Shacklette and Boerngen, 1984. Some metals (e.g., Fe, Cu, Zn) are included in the State Soil Geographic Database (STATSGO) available at: www.nrcs.usda.gov/technial/techtools/stat_browser.html. These data can be grouped at whatever spatial scale is required, but are not screened for whether they represent true background concentrations.

***Recommendations*:**

- Use of a single number to represent background concentration for metals all areas within the U.S. is of limited value due to high variability across such a large geographic area.
- Averages (and ranges) of background concentrations for various ecoregions should be defined (Bailey, 1998; Hargrove and Hoffman, 1999; Omernick, 1986).
- If ecoregion-specific information is not available, a recommended default when conducting national scale assessments is to use state averages

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- Be sure to always define the range that might be encountered within the spatial scale being considered.
- For a site-specific release of a highly bioavailable form of a metal, the background concentration may be ignored.
- For areas of contamination where added metals have aged significantly, consideration of reductions in bioavailability is recommended. Thus, it becomes important to measure exposure in terms of the bioavailable fraction.
- For site-specific risk assessments, it may not be necessary to consider background concentrations during the initial screen; bulk soil concentrations should be compared directly with derived toxicity thresholds for soil organisms.
- For the metal-organism-pathways that do not pass the initial screen, site-specific bioavailability adjustments to bulk soil concentrations often compensate for background metals (that have significantly lower bioavailability).
- Natural background levels should be taken into consideration during any remediation decisions, as reducing soil metals below naturally-occurring values will alter the plant and soil invertebrate community composition, potentially as dramatically as did the anthropogenically elevated soil levels.

4.2.2.2. Soil Invertebrates and Plants

Recommendations:

- Use bulk soil concentrations collected in the top 0–12 cm of soil can be used as an initial estimate of exposure for soil organisms for all types of assessments
- It is recommended that bulk soil concentrations be adjusted to account for bioavailability factors at higher tier assessments; bioassays using site soils are encouraged for areas that do not meet initial screening level values.
- In higher-tier assessments, the organic matter on top of the soil (the “duff”) should be analyzed separately to provide further detail on exposure to detritivores (such as *Collembola*) and deeper-soil-dwelling organisms (e.g., various species of earthworms).

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- Laboratory test data should be normalized on the basis of pH and CEC prior to use in criteria development or hazard ranking. If CEC is not available, adjustments with OM will be qualitatively similar.
- Most accurate estimates of exposures are generally achieved through measuring or modeling concentration of metals in soil pore water.
- Use of metalloregions for national level assessments is encouraged to account for natural background levels and consequent adaptation of soil organisms.
- Remediation values should not be below natural background.

4.2.2.3. Plants (additional recommendations)

Recommendations:

- Aerial deposition of metals onto leaf surfaces can be assumed inconsequential for plant exposure.
- General categories of uptake based on bioavailability of metals to plants are shown in Section 3.
- Strongly acidic soils can be assumed to increase plant uptake of Zn, Cd, Ni, Mn, and Co, and increase the potential for phytotoxicity from Cu, Zn, and Ni.
- Alkaline soil pH can be assumed to increase uptake of Mo and Se, while it can be assumed that Pb and Cr are not absorbed to any significant extent at any pH.

4.2.2.3. Wildlife

Recommendations:

- Food and the incidental ingestion of soil are the two most important exposure pathways for terrestrial wildlife.
- Under most situations, inhalation or dermal pathways may be considered insignificant contributors to total metal loads.
- Tables 12 and 13 in Section 3 provide general estimates of relative importance of soil vs. food chain exposures for various wildlife and geographic regions.
- Incidental ingestion of soil becomes proportionally more important for exposure to wildlife when (1) the BAF from soil to food (e.g., to plants or soil

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invertebrates) is less than 1 and (2) the fraction of soil in the diet is greater than 1%.

4.2.2.4. Food Chain Modeling

Food chain modeling is used to estimate the exposure of wildlife to metals based on ingestion of soil, food, and water. The basic format of the model is the same as that for organic substances; detailed explanations are available in several related documents (e.g., EcoSSLs (http://www.epa.gov/ecotox/ecossl/), ECOFRAM (http://www.epa.gov/oppefed1/ecorisk/index.htm)). Measured concentrations of metals in soil, surface water, and food items can be used in the model, or concentrations in food can be modeled using trophic transfer factors. Information on diet, foraging area, and the like is found in U.S. EPA (1993). The absorbed fraction variables accounts for differences in relative bioavailability for ingested soil and for food. It is either 1 (default value) or an appropriate site-specific estimate. Very little information is available on dietary bioavailability for most wildlife species particularly due to differences in digestive physiology and anatomy across the broad and diverse range of mammalian and avian species. General guidelines are provided for some metals (e.g., lead) in NRC (1980), and human-derived values can be used as default values in the absence of species-specific data.

Recommendations:

- Food chain modeling should be used in national criteria setting or hazard ranking exercises following approaches and default values detailed in the U.S. EPA EcoSSL documentation (U.S. EPA, 2003).
- For site-specific risk assessments, a weight-of-evidence approach is recommended that begins with using default parameters in the standard food chain models and then successively adds more site-relevant data as particular species-exposure route combinations are not screened out (see Fairbrother, 2003 for methodology).

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4.2.2.5. Bioaccumulation

Recommendations:

- The use of single point BCF/BAF in national ranking and categorization should be used with appropriate caution and recognition of the limitations and uncertainty.
- For national level assessments, equations from Sample et al. (1998a) for soil uptake factors for soil invertebrates and for vermivorous wildlife (e.g., song birds, voles, and shrews), and from Efryomsen et al. (2001) for plant uptake factors should be used.
- Soil parameter values from the 5th - 95th percentile of the area of concern should be used to bound the possible uptake rates (alternatively, Monte Carlo approaches can be used, assuming appropriate distributions for each of the parameter values).
- Site-specific assessments should use measured soil parameter values if using models for screening level assessments, and either measured values of metals soil organisms or site-specific bioassays to determine uptake rates for detailed assessments (see Fairbrother, 2003).
- The highest accumulation of metals in plants occurs in the roots and except for hyperaccumulator species, most plant trophic transfer rates can be assumed to be <10.
- Plants are quite sensitive to some metals and may die before achieving levels high enough to be toxic to animals (see Section 3).

4.2.3. Toxicity Assessment – Recommendations

4.2.3.1. Adaptation and Acclimation

- For national scale assessments, the country should be subdivided into metalloregions, 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.
- For site specific assessments, the concepts of pollution-induced community tolerance (PICT) can be applied.

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- All reports of toxicity effects used in setting toxicity reference values (TRVs) or benchmarks, whether for generally applicable national assessments or for site specific assessments, should be critically examined for information about how test organisms were raised and housed.
- For national scale assessments, organisms should be acclimated to standard soils or (preferentially) to the various metalloregion soils.
- For site-specific assessments, acclimation should take place in soils with similar characteristics (e.g., % clay, pH, CEC) as the site of concern.

4.2.3.2. Essentiality

- Consult Table 16 in Section 3 to identify which metals are required as micronutrients for normal organism metabolic function for plants and wildlife.
- Derived toxicity threshold values for essential elements should be used in screening level risk assessments for both national and site-specific applications, if they are no more than 10-fold lower than the nutritional requirements. Otherwise, the required levels should be used as a threshold for allowable exposures.
- Higher tiered assessments may require additional bioassays to characterize the biphasic dose response curve and determine both required and excessive threshold levels.
- For wildlife, the literature on dietary requirements of essential elements for livestock can be consulted. The National Research Council has published useful summaries (NRC, 1980, 1994), and a recent publication updates this information (McDowell, 2003).
- Minimum concentrations required for plant growth are summarized in Epstein (1965, 1972) and Kabata-Pendias and Pendias (2002).

4.2.3.3. Metals Mixtures

- Metals that have the same mode of action can initially be assumed to be additive in effect.

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- For those metals with assumed additivity, either Concentration Addition or Effects Addition models can be used (see Section 3.x for descriptions of these models).
- Effect Addition models, especially if based on body or tissue concentrations, are more accurate than Concentration Addition models, but require reliable dose-response and bioaccumulation curves for all single metals and then careful testing of the models.
- National criteria for mixtures may not be possible, as the combined effects depend upon relative amounts of each metal and their relative bioavailability.

4.2.3.4. Toxicity Testing

- Existing toxicity data for soil organisms (plants and invertebrates) should be adjusted on the basis of CEC and pH to account for bioavailablity differences prior to use in any type of risk assessment or hazard ranking.
- Aging of metals in soils can be taken into account by reducing laboratory-derived toxicity values (e.g., by dividing by a factor of 3 as recently adopted by the European Union), or by including appropriate adjustments in toxicity tests, except when assessing acute (short-term) risks of spills.
- Comparison of field data with laboratory toxicity response information is best done through measuring metals in soil porewater from field assessments and comparing such data to spiked laboratory soils.
- Use of critical tissue residues as an alternative approach to toxicity endpoints is conceptually sound, but requires significant research before critical tissue levels can be established. An exception to this is for some essential elements in plants, where deficiency / sufficiency concentrations in foliage have been developed.

4.2.3.5. Extrapolation of Effects

- Methods for extrapolating toxicity thresholds among species (e.g., species sensitivity distrubtions; SSDs) are the same for metals as those used for organic substances and are subject to the same assumptions of physiological similarities

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and degree of required margin of safety (see U.S. EPA, 2003 for a review of methods).

- All extrapolations should account for different requirements for essential elements and the factors that modify metal toxicity (e.g., acclimation, essentiality, mixtures, etc.).
- Species sensitivity distributions (SSDs) (Van Straalen, 2001; Posthuma, 2001) should be used for extrapolating effects-data among species.
- A review of cross-species extrapolation methods can be found in U.S. EPA (2003).
- Across metal extrapolations (even within the same species) should be avoided, unless mechanisms of action are known to be similar.
- For soil invertebrates, extrapolating toxic response to one metal to potential effects of a non-tested metal can be done using Quantitative Ion Character-Activity Relationships (QICARS) (Newman et al., 1996 - 2000; Lewis et al., 2000).
- For plants and wildlife, there is sufficient information about modes of action of most common metals to make informed judgements about relative toxicity, so empirical extrapolation models such as QICARS would be applicable only for initial screens of minor elements.

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Table 23 presents a qualitative guide on the appropriate use of the recommendations for a particular assessment level. While it is recognized that within an assessment level the types of assessment can vary in detail from simple screening analyses to highly complex studies, the general trend in the application of metal specific methods will increase from ranking to national criteria to site specific assessments.

Table 23. Application of Terrestrial Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Fate & Transport	Incorporate soil residence time (inverse of log K_d) into schemes.	The application of single partition coefficient (K_d)values may be used, as a first approximation K_d values may be developed from MINTEQ or taken from look-up tables (U.S. EPA, 1998; 1999b).	Develop site-specific K_d's.
Transformations	Rank on basis of toxicity of inorganic forms.	Assume negligable.	Assume negligable, except for volatilization of organometalloids during fate estimations.
Background Concentrations	Not applicable when ranking and categorization are based on hazard only.	Metalloregion concept should be used.	Screening Level - Background may be Ignored. Higher Tier Assessments – Use "added risk" approach after normalizing for bioavailability differences.

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Table 26. Application of Terrestrial Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Soil Invertebrate Exposure	Not applicable when ranking and categorization are based on hazard only.	Bulk soil concentrations should be adjusted on cation exchange capacity (CEC) and pH.	Screening Level – Bulk soil concentrations should be adjusted by CEC. Higher Tier Assessments – Site-specific bioassays.
Plant Exposure	Not applicable when ranking and categorization are based on hazard only	Bulk soil concentrations should be adjusted on CEC and pH.	Screening Level – Bulk soil concentrations should be adjusted by CEC. Higher Tier Assessments – Site-specific bioassays.
Wildlife Exposure	Not applicable when ranking and categorization are based on hazard only	Tables 12-13 can be used to identify feeding guild at greatest risk and whether soil ingestion is primary exposure route of food chain modeling is required.	Tables 12-13 can be used to identify feeding guild at greatest risk and whether soil ingestion is primary exposure route of foodchain modeling is required.
Food Chain Modeling	Standard food chain model with default parameters can be used to “back calculate” safe soil values and rank.	Standard food chain model with default parameters can be used.	Screening Level – Standard food chain model with default parameters can be used. Higher Tiers – Site-specific data can be generated for a WOE approach (see Fairbrother, 2003)

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Table 26. Application of Terrestrial Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Bioaccumulation	Log K_d could be used to predict how long metal will remain in the soil; Longer persisting metals have higher potential risk.	The uptake regressions for plants and invertebrate (Sample et al. 1998a and Efroymsen et al., 2001) most appropriate for each metalloregion should be given preference.	The uptake regressions for plants and invertebrate (Sample et al. 1998a and Efroymsen et al.2001) most appropriate for each metalloregion should be given preference. Higher Level Assessments – Site-specific information can be used to parameterize uptake equations (see above refs) or metal concentrations in different parts of the food chain can be mearsured directly.
Adaptation & Acclimation	Not applicable when ranking and categorization generally are based on short-term hazard.	Use metalloregions and acclimate organisms to standard soils or (preferentially) to the various metalloregion soils is recommended prior to initiating toxicity tests. For existing data, adjust for CEC and pH.	Tests of toxicity effects warrant critical examination for information about how test organisms were raised and housed; acclimation should take place in soils with similar characteristics (e.g., % clay, pH, CEC) as the site of concern.

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Table 26. Application of Terrestrial Tools to Metals Assessment Levels

	Tools	Ranking/Categorization	National	Site Specific
1	Essentiality	Derived toxicity thresholds can be used if they are no more than 10-fold lower than the nutritional requirements; otherwise, use the required level.	Derived toxicity threshold values should be used if they are no more than 10-fold lower than the nutritional requirements. Otherwise, the required levels should be used as a threshold for allowable exposures.	Derived toxicity threshold values should be used if they are no more than 10-fold lower than the nutritional requirements. Otherwise, the required levels should be used as a threshold for allowable exposures.
2	Metals Mixtures	Not applicable; Combined effects depend upon relative amounts of each metal.	May not be possible, as the combined effects depend upon relative amounts of each metal.	Use of the Concentration Addition approach in screening level assessments for metals with the same mechanism of action is recommended. Qualitative adjustments may be made to the metal-specific risk quotients using published information on the sign of the metal interactions (potentiation or amelioration).

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Table 26. Application of Terrestrial Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Toxicity Testing	Published toxicity data should be adjusted for bioavailability differences using soil CEC and pH. [Note: The issue of how to account for aging of metals in soils, and associated lab-to-field adjustments/safety factors, will be the subject of deliberation at the upcoming peer consultation workshop.]	Published toxicity data should be adjusted for bioavailability differences using soil CEC and pH. [Note: The issue of how to account for aging of metals in soils, and associated lab-to-field adjustments/safety factors, will be the subject of deliberation at the upcoming peer consultation workshop.]	Adjust published toxicity data for bioavailability differences using soil CEC and pH. [Note: The issue of how to account for aging of metals in soils, and associated lab-to-field adjustments/safety factors, will be the subject of deliberation at the upcoming peer consultation workshop.]
Extrapolation of Effects	For soil invertebrates, plants, and wildlife the use of SSDs is encouraged (different distributions for each organism group).	For soil invertebrates, plants, and wildlife the use of SSDs is encouraged (different distributions for each organism group) QICARs may be used to extrapolate among metals, esp. for soil invertebrates.	Screening Level – For soil invertebrates, plants, and wildlife the use of SSDs is encouraged (different distributions for each organism group). Most sensitive organism may be used for higher tier screens. QICARs may be used to extrapolate among metals, esp. for soil invertebrates.

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4.3. HUMAN HEALTH ASSESSMENT TOOLS FOR METALS

Assessment of risks of metals to human health is similar to conducting assessments of organic substances, with the exception of accounting for naturally occurring background concentrations, the essentiality of some metals, and the fact that metals always occur in combination. Additionally, certain properties associated with toxicokinetics, carcinogenesis, sensitivity of particular subgroups, and delayed toxicity are unique to metals. Data from standard toxicity tests need to be interpreted appropriately in light of these metal-specific attributes. Tools are available for addressing most of these metal-specific attributes during a human health risk assessment.

4.3.1. Fate & Transport

Recommendations for assessing movement of metals through the aquatic or terrestrial environments (water, soil, and sediment) and within the human food chain (i.e., fate and transport models) are the same as those provided above for Terrestrial and Aquatic Ecosystems, section 4.1 and 4.2. Source apportionment and atmospheric transport are covered here.

4.3.1.1. Atmospheric Fate and Transport

A substantial part of the atmospheric chemistry of metals takes place in the aqueous phase, where it is not significantly different from aqueous chemistry in other media. Models and pH/Eh diagrams may be used to determine metal speciation in atmospheric aquatic aerosols. However, due to assumptions of chemical equilibrium, the application of such diagrams and models should be limited to describing metal speciation reactions that can equilibrate in seconds or less. These include many acid/base and metal complex formation reactions but not most reactions involving adsorption, oxidation/ reduction, or mineral precipitation. Atmospheric metal reactions that take longer to equilibrate must be studied in terms of their reaction kinetics rather than equilibrium chemistry.

Deposition is primarily a function of the properties of particulates, deposition can be a significant source of metals into aquatic systems and to humans through exposure to dust. Dias

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and Edwards (2003) describe an approach in which the various available source apportionment methods are used simultaneously to increase reliability and confidence in the source apportionment procedure. This weight of evidence approach involves dispersion models, receptor models, and field data collection. Dispersion models that combine emission inventories and meteorological conditions are used to make predictions. Receptor models that use the chemical characteristics of both potential sources and of samples collected down-wind provide real data for ground-truthing those predictions and can include information on size differentiation, elemental ratios, enrichment factors, temporal and spatial trends. Multivariate data analyses, such as factor analysis, or its variants, enable summarization and interpretation of these various components (Chapman and Dias, 2003).

***Recommendations*:**

- Models and pH/Eh diagrams may be used to determine metal speciation in atmospheric aquatic aerosols.
- For source apportionment, an approach that includes dispersion models, receptor models, and sampling may provide appropriate estimates of deposition.

4.3.2. Exposure Assessment

Assessment of human exposures to any chemical agent includes (1) identifying pathways by which chemicals in the environment can make contact with humans, (2) determining the concentrations of the chemical agent in all relevant physical and chemical forms and in the primary media of human contact, (3) estimating intake rates and amounts in those media through all relevant physiological routes of entry to the body, (4) describing and, where possible, quantifying relationships between exposure concentrations and intakes, and (5) identifying sources of uncertainty and natural variability and, where possible, quantifying these in estimates of exposure.

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4.3.2.1. Background

Recommendations:

- The contribution of the background level of a metal(s) to the cumulative exposure of people should be normalized for bioavailability and speciation, so that only the bioavailable fractions of each source or exposure route are added when calculating total exposure.
- For national level assessments or hazard ranking, contribution from background metals should be considered negligible.
- Site-specific risk assessments should account for background levels of metals in dietary items, water, or air (for inhalation estimates).
- Section 2.2 on bioavailability and section 3.1 on speciation, and aging of metals should be reviewed prior to estimating biologically significant background concentrations.
- In the absence of empirical data, speciation models such as MINTEQ or WHAM may be used to estimate relative ratios of metal species from which inferences can be drawn about bioavailability (e.g, oxides generally are significantly less bioavailable than chloride or sulfate salts).
- Degree of solubility also can be used as a surrogate for relative bioavailability. Such information should be included qualitatively in the final risk assessment, if quantitative information for calculating total exposure to bioavailable fractions is not available.

4.3.2.2. Air Pathway and Inhalation Exposure

Metals are ubiquitous components of particles in ambient air and are emitted by numerous natural and anthropogenic sources. Significant metals emission sources include natural emissions such as, volcanic eruptions and emissions, entrainment of soil and dust, entrainment of sea salt spray, natural forest fires, and man made emissions such as, fuel combustion and smelting. Most metals are removed from the atmosphere by deposition and many metals, with mercury as an exception, have relatively short atmospheric half-lives.

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Inhalation is the major pathway for human intakes of metals in which air serves as the primary medium of contact. Human exposures to airborne metals or other contaminants are usually to metal-bearing particles in the PM 2.5 or 10 fraction (i.e., particles that mass median diameter less than or equal to either 2.5 or 10 microns in diameter); larger particles do not penetrate far enough into the respiratory tract to be absorbed. As was discussed in section 3.3 and 4.3, species- specific toxicity of a metal will vary widely depending on its form. Currently, the emissions and exposure data for metals are typically reported as a total elemental metal or, occasionally, as metal categories (e.g., sulfides of nickel or nickel compounds) but not as a specific species. Improvements in the linkage of metal forms of airborne metals in the breathing zone to toxicity data is needed. Lack of information about particle sizes, chemical form, and solubility of airborne metals in the breathing zone has important implications for accurate modeling of rates of absorption and subsequent internal dose (Khoury and Diamond, 2003).

***Recommendations*:**

- To improve exposure assessments improved information about particle sizes, chemical form, and solubility of airborne metals in the breathing zone will increase the accuracy of modeling of rates of absorption and subsequent internal dose.

4.3.2.3. Soil Pathway and Dietary Exposure

There are three approaches to assessing exposure through the dietary pathway: 1) conduct a food monitoring survey to measure concentrations of metals in individual foods and couple this information with data about food consumption rates for each major food group (i.e., the amount of food that is eaten and the length of time that exposure is expected to occur; food consumption rates are in U.S. EPA, 1997); 2) surveys of actual consumption; and 3) use of exposure modeling coupled with fate and transport modeling (e.g., TRIM.FaTE model). EPA's Dietary Exposure Potential Model (DEPM) links national food consumption and chemical residue data to allow estimates of average dietary intakes of metals and other food contaminants (Tomerlin et al., 1997). An additional approach is to use biomarkers which are measured

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concentrations of metals in urine, feces or other tissues that have known associations to ingestion rates (see Clayton et al., 1999, 2002; Choudhury et al., 2001 for metals and associated tissues for which such information is available). This method is valuable because it provides a direct measure of individual exposure rates.

Recommendations:

- Humans are exposed to metals in surface dust and soil primary through incidental ingestion or from inhalation of suspended dust particles.
- Dermal contact with metals in soil, due to relatively low lipid solubility of most metals, generally can be ignored.
- Exposure amounts from soil ingestion can be adjusted for bioavailability prior to adding to intake from other exposure routes.
- For children, the amount of soil ingested varies with age, activity patterns, and accessibility to soil and dust. Current estimates have been based on short-term measurements and may not accurately reflect long-term trends.
- Pica behavior is recommended for inclusion as a separate exposure scenario
- Four attributes are recommended for consideration when estimating soil exposure: 1) volume of soil (area × depth) to which an individual could be exposed; 2) potential duration of exposure; 3) amount of soil ingested; and 4) bioavailability of metal in soil.
- It is recommended that site-specific exposure assessments measure soil metal concentrations at the depth appropriate to the metal(s) of concern and human receptor behaviors; a default value of 0 to 5 cm is recommended.
- Exposure estimates based on national dietary and food residue surveys are most applicable for national scale assessments
- Surveys of actual food consumption patterns, coupled with measurements of metal concentrations in the various foods, are particularly valuable when conducting assessments of risks to subsistence farmers or anglers or ethnic

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populations whose dietary habits differ significantly from those of the general population.

4.3.2.4. Water Pathway and Oral Exposure

Humans, consume water specifically treated for human consumption (i.e., drinking water); thus, the exposure context of metals in human drinking water will be very different from that of ambient water. Inorganic forms of metals in drinking water will consist of the more bioavailable, water-soluble species. People can be exposed to metals dissolved in ambient surface water during swimming or other recreational activities or during various occupational activities. Children can be particularly vulnerable to exposure to sediment-borne metals as a result of swimming or play activities at or near the shoreline. Estimation of intake of metals in drinking water requires information about concentrations of metals in the water and the amount of water consumed. Metal concentrations in drinking waters are measured at the distribution point for municipal water delivery systems. The contribution of metals from pipes (either from the distribution system to the home or within the home) is rarely assessed. Water delivered from private wells or ambient surface waters may contain higher levels of organic carbon or other ligands to which metals can bind, thereby requiring an adjustment to account for differential bioavailability of the dissolved metals. These factors can be incorporated into site-specific assessments, but local data will need to be collected on a case-by-case basis.

***Recommendations*:**

- National exposure assessments can be made on the basis of information from municipal water systems on concentrations of metals in drinking water.
- Uncertainties will include regional differences in bioavailability of metals due to variation in water characteristics (e.g., hardness), the contribution of household distribution systems to total metal load at the tap, and lack of information from households on private wells.
- It is recommended that site-specific assessments should use measured metal concentrations at the tap.

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- Data on tap water consumption rates for the general population are located in the EPA publication estimating per capita water ingestion in the US (EPA, 2000).
- Dermal absorption during swimming or showering is a negligible exposure pathway and generally can be ignored.

4.3.2.5. Transplacental Exposure

Maternal exposure can result in transplacental transfer of metals or transfer through breast milk (for organometallics). This can be a particularly important exposure pathway for metals that accumulate in bone (e.g., lead, strontium, uranium) because of mobilization of bone minerals during pregnancy.

***Recommendations*:**

- Pharmacokinetics models of lead transplacental transfer are recommended for screening level assessments (U.S. EPA, 1994, 1996.). National assessments can also use these models, although default assumptions may be needed in lieu of specific, nationally relevant data. .
- Similar models for other metals are not available, at this time, so transplacental transfer cannot be estimated.

4.3.2.6. Lead Exposure Models

The Integrated Exposure Uptake Biokinetic Model (IEUBK) model is designed to predict the probable blood lead concentrations for children between 6 months and 7 years of age who have been exposed to lead through environmental media (air, water, soil, dust, and diet), and the probability that these concentrations will exceed 10 μg Pb/dL. It standardizes exposure by assuming age-weighted parameters for intake of food, water, soil, and dust. The model simulates continual growth under constant exposure levels (on a year-to-year basis). The model also simulates lead uptake, distribution within the body, and elimination from the body. The IEUBK model allows the user to input relevant absorption parameters (e.g., the fraction of lead absorbed from water) as well as intake and exposure rates.

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***Recommendations*:**

- The IEUBK model for lead in children is recommended for use in all site-specific assessments. It is available on line at: http://www.epa.gov/superfund/programs/lead/ieubk.htm.
- Models linking adult exposures and blood lead concentrations are available in Bowers et al., 1994; Carlisle and Wade, 1992; Carlisle, 2000; Stern, 1994, 1996; U.S. EPA, 1996.
- IEUBK accounts for lead accumulation resulting from differential rates of uptake and elimination. Accumulation of other metals will require similar PBTK models.

4.3.2.7. Related Exposure Modeling Tools

A more generic exposure model, RESRAD, was developed by the U.S. Department of Energy for risk assessment of radionuclides in soil, and is available at http://web.ead.anl.gov/resrad/home2/. It includes functionality for Monte Carlo simulation. While the entire model is not applicable to metals, the extensive human exposure module is applicable to other metal contaminants. Other exposure models that may be used with metals include the EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model (Zartarian et al., 2000); and Lifeline (http://www.epa.gov/oscpmont/sap/2001/march28/lifeline.pdf). These models are useful for screening level assessments or for generalized estimates of national exposures. They do not account or metal-specific properties such as bioavailability, so large uncertainty will be associated with the model estimates. TRIM.Expo$_{inhalation}$ model (http://www.epa.gov/ttn/fera/human_apex.html) is applicable for metals when estimating exposure via the inhalation route.

4.3.2.8. Bioavailability

Evaluating bioavailability for the ingestion route is important because a given dose of a metal in an environmental medium may be absorbed to a different extent than the same dose administered in the study used to derive a toxicity value (e.g., oral reference dose (RfD) or cancer slope factor (CSF)). However, the RfD and CSF are typically developed from laboratory toxicity

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tests using highly bioavailable forms, and are based on administered rather than absorbed doses. Because the relative bioavailability of metals in food or ingested soil media frequently differs from that in laboratory studies, risks from ingestion of the metal might be either over- or under estimated if equivalenc. Thus, it is important to adjust all exposures by their relative bioavailability so total exposure is summed correctly and can be appropriately compared to the effects value. Further discussions on bioavailability issues are presented in Sections 2.2 and 3.4 and Drexler et al. (2003) and NRC (2002).

***Recommendations*:**

- For national level and screening level site specific assessments, the bioavailability of the metal exposure from the site can be assumed to be the same as the bioavailability of the source used to derive the toxicity value (RfD or CSF)
- For higher tier risk assessments, development of a medium-specific default absorption factor may be appropriate.
- If sufficient data are available, then RfDs that are specific for an exposure medium can be derived that account for bioavailability.
- The juvenile swine model presently is the preferred animal model for lead (U.S. EPA, 1999).
- In-vitro methods can be used for screening, and when validated they can be used for assessments on a metal by metal basis.

4.3.3. Effects Analysis

4.3.3.1. Essentiality

Seven metals are known to be nutritionally essential for humans, and four others have possible beneficial effects (Table 21). Health problems occur if essential trace elements are either deficient or present in excess.

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***Recommendations*:**

- It is recommended that National assessments for criteria setting or other purposes and site-specific assessments account for the essentiality of some metals.
- In setting reference values (RfCs/RfDs) the recommended dietary allowance (RDA) should be taken into consideration.
- For essential elements, risk assessors are strongly recommended to critically review the use of uncertainty factors (i.e., those applied for animal-to-human extrapolations or for acute-to-chronic concerns).
- RDA's can be found in material provided by the Food and Nutrition Board of the National Academy of Sciences (NAS/IOM, 2001).
- Additional guidance on methods for assessing risks from excessive exposure to nutritionally essential metals is provided by the World Health Organization (WHO/IPCS, 2002).

4.3.3.2. Cancer

At least five transition metals or metalloids — arsenic (through drinking water exposure), cadmium, chromium VI (due to injections), beryllium, and nickel (from pulmonary or, in some cases, dermal exposures) — are accepted as human carcinogens in one form or another or in particular routes of exposure (NTP, 2002). Target organ sites for metals as carcinogens are summarized by Waalkes (1995). EPA's Guidelines for Cancer Risk Assessment (U.S. EPA 1999) pertain to all substances being assessed for carcinogenicity, including metals, for the purposes of national level or deailed site-specific assessments. These gudelines currently are in revision (e.g., U.S. EPA, 2003).

***Recommendations*:**

- For the five metals for which carcinogenicity data exist, national criteria setting or site-specific assessments can account for carcinogencity.
- Methods are available in U.S. EPA, 1999.

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4.3.3.3. Metals Mixtures

Metals are normally found in the environment as mixtures, and risks may be mitigated or enhanced by their interactions. There are three classes of interactions between metals: between essential metals, between toxic metals, and between essential and toxic metals. There are three classes of interactions between metals: 1) between essential metals; 2) between toxic metals; and 3) between essential and toxic metals. The weight-of-evidence (WOE) approach can be used to adjust the hazard index for each metal in a mixture. This approach is also known as the interaction-based hazard index (Hertzberg et al. 2002, U.S. EPA, 2000b). The hazard index for each metal is quantitatively adjusted for interactions on the basis of binary combinations of metals.

***Recommendations*:**

- When empirical data on effects of metals mixtures are available, it is recommended that the toxic threshold of the mixture be used.
- The default approach is to assume dose additivity for individual metals. This approach is most appropriate for chemicals that produce the same effects by similar modes of action.
- In the case of metals with known differences in critical effects, separate effect-assessments are encouraged for each metal. Interactive effects (e.g., synergism, antagonism) should be included if information as available, or acknowledged as a source of uncertainty.

4.3.3.4. Sensitive Sub-Populations and Life Stages

Certain subgroups of human populations may be uniquely sensitive to adverse effects resulting from exposure to particular metals. These may include various life stages (fetus, child, adult, elderly) and of different genders, those having genetic polymorphisms or pre-existing diseases, and those that differ in nutritional status and lifestyle choices. For metals, particularly

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those that are nutritionally essential, differences in pharmacokinetic behavior among these groups become very important and warrant special consideration.

There is minimal information on the types of susceptible subpopulations and life stages that may exist with regard to exposure to metals. The only way to determine whether a susceptible subpopulation exists is to examine the dose-response effects in the various segments (life stage, gender, health, nutritional status, etc.) of the total exposed population. More information about the metal, including its toxicokinetics, similarity of effects in more than one animal species or humans, mode of action, and temporal relationship (time between exposure and effect) will aid in determining whether additional safety factors should be added in the assessment (U.S. EPA, 2002).

***Recommendations*:**

- For metals, as with other agents, Agency risk assessments should consider subpopulations with differing sensitivities that may arise as a result of differential exposure or susceptibility.
- For metals that are known to affect sensitive subpopulations differentially (e.g., genetic predisposition to copper poisoning, childhood sensitivity to developmental effects of lead), specific no observable adverse effect levels (NOAELs) should be developed, or a benchmark dose (BMD) approach used, for these particular subpopulations.

4.3.3.5. Pharmacokinetic Data and PBPK Models

Physiologically based pharmacokinetic (PBPK) models are additional tools that can be used to evaluate the relationship of dose metrics and the toxic effect of concern, and can help guide the selection of an appropriate dose metric. A dose metric is a measure of the amount or concentration of the active form of metal supplied to the target organ or tissue over an appropriate time period.

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***Recommendations*:**

- PBPK models are used in developing quantitative dose-response assessment for cancer risk and may be used for RfD/RfC development as well as higher-tier site-specific assessments. .
- Additional research is needed before PBPK models can be applied effectively to inorganic metal assessments.
- Other methods include use of simple default adjustments (e.g., application of default uncertainty factors) or use of categorical default adjustments (e.g., dosimetric adjustments applying to a range of metals or metal species on the basis of similarities in solubility, bioavailability, toxicity, etc.).
- It is recommended that evaluation of the extant pharmacokinetic database for any metal explicitly consider the issues discussed in Section 3.4 and Goyer et al. (2003).
- Application of a PBPK model to risk assessment should satisfy the following key criteria: (1) identifying toxic or active form(s) of the metal, (2) selecting the appropriate dose metric, and (3) identifying appropriate target organ or cells on the basis of the health effect of greatest concern.
- It is recommended that the toxic endpoint must be matched with the active form of the metal (e.g., mercury versus methyl mercury).

4.3.3.6. Toxicity Testing

Toxicity values for metals occur within the same databases as those for other compounds. The primary database for human health toxicity values is the Integrated Risk Information System (IRIS) maintained by EPA (http://www.epa.gov/iris/). The IRIS program provides 42 metal-associated RfDs. Some RfDs identify a general subcategory of the metal (inorganic, soluble, elemental), but most do not differentiate among metal species. However, to achieve an adequate internal dose for the study of toxicity, animal toxicologists often use bioavailable form of metals. A major challenge is that exposure data for metals typically are reported as a total elemental

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metal or, occasionally, as metal categories (e.g., sulfides of nickel or nickel compounds) but not as a specific species (e.g., nickel subsulfide). Risk assessors then are faced with comparing toxicity data generated from exposure to a highly bioavailable metal form to environmental exposures of less available metals.

***Recommendations*:**

- See bioavailability recommendations in section 4.4.2.
- It is recommended that adjunct scientific data be used to adjust the dose identified in the animal study to account for differences in bioavailability and toxicity of different metal species.
- The preferred approach is to conduct new animal toxicology studies using the metal form encountered in the environment.
- Toxicity values for 42 metals are available in EPA's Integrated Risk Information System (IRIS) (http://www.epa.gov/iriswebp/iris/index.html).

4.3.3.7. Atmospheric Metals – Bioavailability

EPA assesses risks for lead with a set of pharmacokinetic models known as the integrated exposure uptake biokinetic (IEUBK) and adult lead models (see Section 3.2. Exposure). Although these models explicitly consider ingestion bioavailability of lead, they do not consider inhalation bioavailability. The selection of bioavailability assumptions and defaults should be based on good scientific judgement, and the exposure and toxicity data should be as consistent as possible. New toxicity studies need to be coordinated with parallel efforts to develop methods to sample and speciate priority metal compounds to resolve exposure with toxicity assessments.

The impetus toward a more comprehensive evaluation of metals must start with qualitative and quantitative toxicology. If there is a significant difference among the various atmospheric metal species with respect to toxicology (as is the case with divalent and elemental mercury), then expenditure of resources on environmental fate models, development of analytical techniques, and monitoring may be warranted.

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***Recommendations*:**

- The bioavailability of some inhaled metals can be much higher than that of other routes of intake.
- particulates
- Variations in airway structure and respiratory conditions (e.g., as weith age) may alter the deposition pattern of inhaled particles, which may contribute to variations in bioavailability.
- New toxicity studies need to be coordinated with parallel efforts to develop methods to sample and speciate priority metal compounds to improve exposure and toxicity assessments

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Table 24 presents a qualitative guide on the appropriate use of the recommendations for a particular assessment level. While it is recognized that within an assessment level the types of assessment can vary in their level of detail from simple screening analyses to highly complex studies, the general trend in the application of metal specific methods will increase from ranking to national criteria to site specific assessments.

Table 24. Application of Human Health Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Fate & Transport	See Terrestrial Assessment Tools	See Terrestrial Assessment Tools For atmospheric dispersion, fate and transport, most metals are removed from the atmosphere by deposition and have relatively short atmospheric half-lives. Mercury is a significant example of where this is not true. Due to the oxidizing nature of the atmosphere, metals are often converted to their most oxidized stable forms	See Terrestrial Assessment Tools For atmospheric analysis, an approach that includes dispersion models, receptor models, and sampling may provide appropriate estimates of deposition
Background concentrations	Negligible	Negligible, but see Metalloregions in Terrestrial Assessment Tools	Added risk, when relative bioavailability of background metals to metals from other exposure routes is known

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Table 27. Application of Human Health Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Air Pathway and Inhalation Exposure	Not Applicable when ranking and categorization are based on hazard only	Where air serves as the primary medium of contact then inhalation can be assumed to be the major exposure pathway. However, the ingestion of dust also contributes to human intake of metals. Uncertainties in inhalation exposure estimates can be caused by only measuring total metals, as the metal species affects the mechanisms, rate, and extent of absorption in the respiratory tract Toxicity studies need to be coordinated with parallel efforts to develop methods to sample and speciate priority metal compounds to resolve exposure with toxicity assessments. PM10 fraction should be used, and bioavailability should be taken into account, for airborne particulate metals when data are available	Information about particle sizes, chemical form, and solubility of airborne metals in the breathing zone is needed for accurate modeling of rates of absorption Stationary air samplers or personal dosimeters can be used to measure exposure to particulate metals; PM10 faction should be used, taking into account chemical form and solubility.

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Table 27. Application of Human Health Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Soil pathway and dietary exposure	Not Applicable when ranking and categorization are based on hazard only	National dietary and food residue surveys for the general population should be used. Fate and transport models (e.g., TIM.FaTE) also may be used to predict exposures. For assessments of risks to subsistence farmers or anglers, or ethnic populations whose dietary habits differ significantly from those of the general population, specific (measured) dietary surveys are preferred. Default values for soil ingestion (e.g., 0 - 5 cm surface) can be used.	National dietary and food residue surveys can be used in screening level assessments. Detailed site assessments measure actual food consumption and/or metal concentrations. Site-specific scenarios for soil ingestion (depth; extent; duration) are preferred; include pica children when appropriate. Fate and transport models (e.g., TIM.FaTE) also may be used to predict exposures when measured data are not available..
Water pathway and oral exposure	Not applicable when ranking and categorization are based on hazard only	Information from municipal water delivery systems are recommended for use.	Measured metal concentrations at the tap, prior to first flush in the morning are recommended.

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Table 27. Application of Human Health Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Transplacental exposure	Not applicable when ranking and categorization are based on hazard only.	PBPK model available for lead; default values can be used	PBPK model available for lead; site-specific values are recommended for use
Lead exposure	Not applicable when ranking and categorization are based on hazard only.	IEUBK model with default parameters can be used.	IEUBK model available for lead; site-specific values are recommended for use.
Exposure models	Not applicable when ranking and categorization are based on hazard only	SHEDS (for 1 - 6 yr old children), Lifeline, and TRIM.Expo are examples of exposure models that may be used for inhalation assessments.	SHEDS ((for 1 - 6 yr old children)), Lifeline, and TRIM.Expo are examples of exposure models that may be used for inhalation assessments.
Bioavailability	Not applicable	(1) Bioavailability of the metal exposure is assumed to be the same as the bioavailability of the source used to derive the toxicity value. (2) Where sufficient data are available, a medium-specific default absorption factor for the metal of interest can be used	In-vitro methods can be used for screening, when validated they can be used for assessments on a metal by metal basis. Whole animal methods offer definitive results

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Table 27. Application of Human Health Tools to Metals Assessment Levels

	Tools	Ranking/Categorization	National	Site Specific
1	Essentiality	RfC/RfD should consider RDA. RDA may be used as a default in ranking exercises.	Consider RDA when developing RfC/RfD. Acknowledge conservatism if sensative subpopulations are included in RfC.	Consider RDA when developing RfC/RfD. Sensitive subpopulations should be accounted for separately.
2	Carcinogenicity	Applicable only to As (drinking water), Be, Cd, Cr(VI) (injection), Ni (pulmonary, dermal). Ranking should be done only for applicable exposure routes	Standard U.S. EPA carcinogenicity guidelines can be used.	Standard U.S. EPA carcinogenicity guidelines can be used.
3	Delayed effects	Not applicable	Delayed neurotoxicity models developed for organophosphates can be used for neurotoxic metals.	Not generally assessed.

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Table 27. Application of Human Health Tools to Metals Assessment Levels

Tools	Ranking/Categorization	National	Site Specific
Sensative Sub-Populations and Life Stages	Not applicable	Criteria can be developed for separate subgroups, if needed.	Criteria can be developed for separate subgroups, especially children (lead), pregant women (lead, mercury), genetic groups (Wilson's disease for copper). Differential exposure estimates (e.g., pica child) are recommended for inclusion .
PBPK models	Not applicable	May be useful for some metals (e.g., lead transplacental transfer); use default values.	Applicable for detailed assessments, particularly for sensitive subgroups. Site-specific values are recommended.
Toxicity testing	Adjust results so all metals are compared on the basis of the same relative bioavailability	Criteria recommended to be provided as an algorithm, rather than a single number, so they may be adjusted for bioavailability differences between toxicity data and potential exposure information	Results of toxicity tests and exposure estimates should be adjusted so they are compared on the basis of the same relative bioavailability.

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5.0. METALS RESEARCH NEEDS

The field of metals risk assessment has advanced rapidly during the past 5 plus years, as reflected in the large amount of information described in this document. However, significant uncertainties and gaps remain that require additional research if accurate assessments are to be conducted. This section briefly reviews major, on-going research programs within and outside the Agency, and provides a list of recommendations for future research endeavors. This section is not intended to outline a research strategy for metals risk assessment. Rather it discusses the current direction of metals-related research by the EPA, external institutions, and academia, as it relates to uncertainties and gaps in metals risk science.

5.1. U.S. EPA RESEARCH

EPA has significant resources devoted to researching metals-related topics, and a variety of metals-related endeavors are planned and underway in an ongoing effort to better understand the behavior and effects of metals in humans and the environment and to continue to advance the field of metals risk assessment. Specific summaries of metals-related research at EPA are available for viewing on the Agency's Science Inventory, which is a searchable catalog of EPA research, available at http://cfpub.epa.gov/si. In addition, EPA's Office of Research and Development (ORD) has a multi-year planning effort to guide the direction of its research program. The purpose of the multi-year plans (MYPs) are to provide a framework that

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integrates research across ORD's laboratories and centers. The MYP for contaminated sediments describes a number of projects planned and underway that involve current topics and research needs. The most recently available MYPs are available for review at http://www.epa.gov/osp/myp.htm. The following are some examples of Agency research and assessment projects planned and underway involing metals topics: (Placeholder: More examples may be provided)

- Ecological effects of selenium on soil invertebrates to support the development of soil screening limits for selenium (FY2004).
- Ecological assessment of the risks associated with ground water contamination and exposures (FY2005).
- Characterization and assessment of the impact of metals speciation on ecological receptors (FY2006).
- Evaluation of stabilization of metals in sediments (FY2007)
- Evaluation of perturbation on metals speciation and ecological receptors (FY2008)

5.2. External Research

The Metals in the Environment Research Network (MITE-RN) is a network of collaborating institutions with participants from academia, government, and industry, formed in 1998 with the aim of developing a better understanding of sources of metals in the environment, how metals move and transorm within the environment, and how they can affect ecosystems and human health (www.mite-rn.org). MITE-RN has been funded at approximately $7M for the period 1999-2004, with contributions from the Mining Association of Canada, National Sciences and Engineering Research Canada, the Ontario Power Generation Inc., and "in-kind"

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contributions from Environment Canada, Fisheries and Oceans Canada, and Natural Resources Canada as well as funding support from International Lead Zinc Research Organization, the International Copper Association, and Nickel Producer's Environmental Research Organization. MITE-RN has published approximately 30 research articles covering all of the topics discussed in the Framework, (www.mite-rn.org/files/mite-rn_pubs.pdf), with the most recent compilation of papers found in Human and Ecological risk Assessment Vol. 9 (4).

Several universities have established multidisciplinary research centers for metals. For example, under a grant from the National Institutes of Environmental Health Sciences (NIEHS), Harvard University has established the Metals Research Core which promotes innovative research among investigators who are studying the environmental fate and health effects of exposure to metals and related fields, with an emphasis on potential gene-metal, metal nutrient, and metal-metal interactions (www.hsph.harvard.edu/niehs/metals.html). The Agency funds a multi-institutional Center for Study of Metals in the Environment, coordinated out of the University of Delaware and including Colorado School of Mines, Manhattan College, McMaster University, Ohio State University, Oklahoma State University, University of Wyoming, and University of Missouri at Rolla (www.ce.udel.edu/CSME/Index.html). The Center for Air Toxic Metals® (CATM®) at the University of North Dakota Energy & Environmental Research Center (EERC), established in 1992 by the U.S. EPA's Office of Environmental Engineering and Technology, develops information on trace elements hat can be used to develop pollution prevention strategies (www.eerc.und.nodak.edu/catm/). Dartmouth's Toxic Metals Research Center is an interdisciplinary group that studies how arsenic and other metals affect human health and the environment (http://www.dartmouth.edu/~toxmetal/). The Agency also funds the Hazardous Substance Research Centers (HSRCs) which addresses metals-linked topics, such as mining, contaminated sediments, and groundwater contamination. The following are applicable web sites for HSRCs:

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http://www.engr.colostate.edu/hsrc/new.html

http://www.hsrc.org/hsrc/html/ssw/newsletter/sswnews.html

http://wrhsrc.oregonstate.edu/publications/index.htm

The metals industry also sponsors research conducted at both public and private institutions world-wide. Sponsors include: the International Lead Zinc Research Organization (www.ilzro.org), the International Copper Association (www.ica.org), the Nickel Producer's Environmental Research Organization (www.nipera.org), the International Zinc Association (www.iza.org), Eurometeaux, the International Cobalt Association, and the International Council on Mining and Metals (www.icmm.com).

5.3. SPECIFIC RECOMMENDATIONS

The information provided here is a summary of research recommendations provided in the metals issue papers (REFs), together with additional comments provided by reviewers of this Framework.

5.3.1. Environmental Chemistry

In general, environmental chemistry of metals research could benefit from:

- The development of more routine chemical-species-specific analytical methods.
- The development of extraction techniques that have general utility in assessing bioavailability and/or mobility.
- The validation of geochemical and chemical-specific environmental fate and transport models.
- Additional research on metal mobility in soils and the use of partition coefficients.
- Application of HSAB to metal mixtures and toxicity.

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- Increased understanding of metal chemistry in sediments.

5.3.2. Bioaccumulation and Bioavailability

5.3.2.1. Aquatic

- Evaluation of the bioaccumulation of metals bound to colloidal material in ambient water.
- More thorough evaluation of the efflux rates of metals from different animals, including specific tissues, following bioaccumulation from the dissolved phase and from the dietary pathway.
- Evaluation of metal bioaccumulation in aquatic bacteria, which may influence the fluxes of certain metals in aquatic systems and which may introduce metals into bacteria-based food chains.
- For organisms that are used or at least have the potential to serve as bioindicator organisms, a more detailed knowledge base is required on their basic physiology and ecology; further, monitoring programs could focus on key biomarkers of exposure and effects and would be wise to develop an algorithm to calculate an integrated stress index.
- New approaches to evaluate the bioaccumulation of metals from waters in which there are numerous contaminants (such as would be found in most contaminated harbors or rivers) to assess synergistic and antagonistic effects.

5.3.2.2. Terrestrial Soil Organisms

- Development and validation of empirical and mechanistic models linking soil physicochemical characteristics, metal speciation, and toxic effects and bioaccumulation in soil invertebrates (e.g., BLM for soil organisms).

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- Development and validation of kinetics models describing metal bioaccumulation in soil invertebrates.
- Basic research on the physiology of metal metabolism in various groups of soil invertebrates; evaluation of the relevance of soil pore water or diet in exposure and partitioning of metals in soil invertebrates.
- Identification of the risks for predators associated with the consumption of soil invertebrates containing metals; evaluation of the risk of consumption of by predators of metal partitioned to different fractions in soil invertebrates (e.g., storage granules versus metallothionein).
- Development of metal-specific biomarkers capable of quantitatively detecting magnitude and species of metal exposure.

5.3.3. Exposure

Research on exposure issues is best defined in regard to the particular receptors; hence, this section is divided into discussions of exposure research for human, terrestrial, and aquatic organisms.

5.3.3.1. Human Health Receptors

- Research to improve sampling, measurement approaches, and exposure models.
- Research to understand the chemical and physical forms of metals in the primary media of exposure.
- Data on rates of soil and surface dust ingestion, including estimates of central tendencies, both short-term and long-term, inter- and intraindividual variability (e.g., within age- and across ages), and relative contributions of surface dust and soil.

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- Information about the types and frequencies of activities that place children in contact with contaminated soils, dusts, or surfaces (e.g., hand-to-mouth behavior, rates of contact with surfaces).
- Methods to predict concentrations in surface dust, a primary medium of contact, from measurements made in surface soil samples, surface dust wipe samples, and surface dust vacuum samples.
- Better estimates of dietary intakes of metals.
- Information on the contribution of locally harvested foods to metal intakes (e.g., uptake of metals from soil, intakes of home-grown or home-harvested foods).

5.3.3.2. Aquatic Receptors

- Defining the best ways of expressing exposure concentration.
- Accommodating differences in exposure durations.
- Combining exposure concentrations when exposure involves metal mixtures.
- Assessment of relative merits of different methods used to express exposure concentrations in sediments and suspended solids.
- Comparison of the simple extrapolation methods to richer survival or time-to-event models is essential.

5.3.3.2. Terrestrial Receptors

- Further work is needed to define or reduce the associated uncertainty of using generalized wildlife exposure models.
- Develop laboratory test data for soil systems that better reflected the actual forms of metals in field soils.
- Data for terrestrial receptors with on the joint effect of metals in mixtures.

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5.3.4. Human Health Effects

- Research should be conducted to determine potential essential or beneficial effects of metals and inorganic metal compounds (especially as these effects impact low-dose extrapolation).
- There should be further research concerning the potential interactions between essential metals and toxic metals and between toxic metals per se.
- Research should be conducted concerning the applicability of toxicokinetic models for risk assessment for metals nd inorganic metal compounds. Consideration should be given to differences in models for essential metals and toxic metals with no known beneficial effects.
- There should be further research and development regarding the use of gene and protein biomarkers as endpoints in the risk assessment process for regulatory issues.
- Speciation of metals in tissues of target organs should be determined. Research should be conducted on mechanisms of toxicity including carcinogenicity, and whether carcinogenicity of specific metals is a threshold or non-threshold event.
- Research is needed to meet the needs of sensitive individuals on the basis of genetic and developmental factors.

5.3.5. Characterization of Ecological Effects

Because of significant differences in ecology, physiology, and toxicology aquatic and terrestrial organisms, research recommendations are provided separately for each group.

5.3.5.1. Toxicological Research Needs

- *Test Matrix*: Perform tests under conditions that are representative of environmentally relevant exposure conditions to form a basis for development of methods to extrapolate from laboratory to field conditions, and from site to site in

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the field in situations where the water-, sediment-, or soil-quality characteristics are quite variable.

- *Model Development*: Development of descriptive statistical models that establish the boundaries for which the results are applicable. Development of predictive speciation and uptake models, such as the FIAM or Tblm.
- *Test Design*: A concerted effort to generate reasonably complete concentration-response surfaces for metals in major soils representative of larger areas of the continent would be very useful. Test designs should be based on regression models and strive to depict the range of responses from relatively low concentrations to relatively high concentrations.
- *Measurement Endpoints*: Multiple endpoints should be scored over the course of the in-life portion of tests. Data on growth parameters, overall healthiness of test organisms, behavioral, and reproductive endpoints should be explored. Such data could be useful in developing descriptive statistical models, including multiple regressions, clustering analyses, and such. In addition, such data could be used to calibrate predictive models that attempt to relate effects across exposure periods.
- *Interspecies Extrapolation*: Studies designed to develop interspecies extrapolation models, especially for terrestrial organisms.
- Interactions Among Metals: Research to understand interactive effects, for both acute and chronic exposures. Methods for representing the joint effects of metal mixtures on the organism, in the context of the BLM, have been proposed, but these methods have not been implemented nor tested to date.

5.3.5.2. Ecological Research Needs

- *Extrapolations From Laboratory to Field*: Studies documenting the correspondence or lack of correspondence between simple laboratory toxicity tests

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and field assessments are necessary. In situations where laboratory and field results are inconsistent, research is necessary to identify factors that contribute to these differences.

- *Indirect Effects of Metals and Species Interactions*: Studies of the effects of metals on species interactions and their ecological significance.
- *Acclimation and Adaptation to Metals*: Additional research is necessary to understand the cost of tolerance and adaptation to metals, and the potential consequences in regard to exposure to multiple stressors.

5.3.6. Unit World Model for Metals

Recognizing the continuing need to overcome limitations in understanding and, therefore adequately predicting, metal behavior in the environment, it has been proposed that use of a suite of evolving computational modelling tools could provide the basis for metals assessments, particularly for hazard ranking and screening level risk assessments. The model would be run for a generic environment (the "Unit World"), giving output in the form of substance specific loadings that would result in accumulations in target compartments that equal specified toxicity thresholds (e.g., LC_{50}, EC_{25}), known as the "critical load." It is anticipated that such outputs could be used in both classification and priority ranking as well as for regional (or national) screening assessments. For screening assessments, an attempt is made to describe how the substance will behave in the environment, to which media it will partition (e.g., air, soil or water), how long it will persist, in which media it will primarily degrade, and ultimately, what mass input will result in media that will cause a toxic effect. These assessments introduce an illustrative or hypothetical release into a hypothetical, evaluative region of interest. The model yields calculated masses, concentrations and rates of transport and transformation that are entirely fictitious. Features that do not depend on the quantity of chemical or specific

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environmental characteristics, such as environmental persistence, relative importance of degradation and transport pathways, and relative concentrations among media, can be deduced. We should note that the decision point for whether an assessment of toxicity is required is derived through an evaluation of environmental fate processes.

This approach also could be used to conduct a risk assessment in which real emission rates are introduced into a model construct of a real environment in an attempt to calculate real masses and concentrations. These predicted environmental concentrations (e.g., PECs) can be compared with measured values to evaluate the performance of the model, as well as in a comparison with concentrations below which adverse toxicological effects are not expected to occur (e.g., PNECs). This comparison results in an assessment of the risk of an adverse effect at the predicted concentration.

A "critical load" is defined as the mass per unit time of a substance that, when introduced into the environment, results in accumulations in environmental media that reach specified toxicity thresholds. Key inputs are toxicity data (acute or chronic thresholds) for individual environmental compartments, and the physical and chemical properties of the substance. Fate models may be envisaged as being run in reverse to back-calculate the loading that results in achieving the specified toxicity concentration. Processes that affect fate and potential exposure of organisms, such as inter-compartment transfer, complexation, and adsorption and precipitation reactions, are included. Since many of the fate processes that affect metal ions and organic compounds are similar, a common modeling framework may be envisaged for organics and metals, with processes (e.g. biodegration) turned on or off as required depending on the nature of the substance.

> The Unit World Model calculates the mass loading needed to achieve the ***critical load*** of metal in each environmental compartment (soil, sediment, water). A "critical load" is the amount of substance in the environment that results in specified toxicity thresholds.

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The Unit World approach uses models derived from previous modelling efforts for metals for aquatic systems (e.g., Di Toro, 2001, Bhavsar et al., submitted). The aim here is to produce a model that is similar, but which includes the processes that are necessary to describe the behaviour of metals in both aquatic and terrestrial environments simultaneously. The model is not intended to represent a specific location, but rather a representative setting that is typical of the class of environments being evaluated. It also is not intended to be a complete description of metal fate and transport. Rather it focuses on the primary processes that affect the toxicity and long-term fate of metals. It is designed to be used for evaluative purposes, rather than for detailed site specific evaluation.

The model framework is presented in Figure 11. It is composed of an aquatic and terrestrial sector. The model is formulated as a series of mass balance equations that are formulated assuming that the rate of adsorption and desorption are fast relative to the other processes (i.e., the local equilibrium assumption). By contrast, the kinetics of metal sulfide precipitation and dissolution are formulated as kinetic processes. The concentrations and characteristics of the necessary water column and particulate partitioning phases will be established to represent the “unit worlds” to be used in the evaluation.

Partitioning in the water column and aerobic sediment layer is computed using WHAM6/SCAMP (Tipping, 1998; Lofts and Tipping, 1998). These models have been calibrated with laboratory data and have parameters for many of the metals that are of interest. Some field testing has also been performed with reasonable results (Lofts & Tipping, 1998; Bryan et al., 2002). The aqueous phase speciation includes DOC complexation. The particulate partitioning phases are organic carbon, the oxides of Al, Si, Mn and Fe, and a mineral cation exchanger. The concentrations of these particulate phases are specified externally as part of the input parameters. SCAMP assumes that the partitioning to these phases are additive. The importance of metal sulfide precipitation in the anaerobic layer and subsequent oxidation in the aerobic layer is well known and models of these phenomena have been developed (e.g. Boudreau, 1991; Di Toro et al., 1996). Therefore, these reactions are modeled explicitly.

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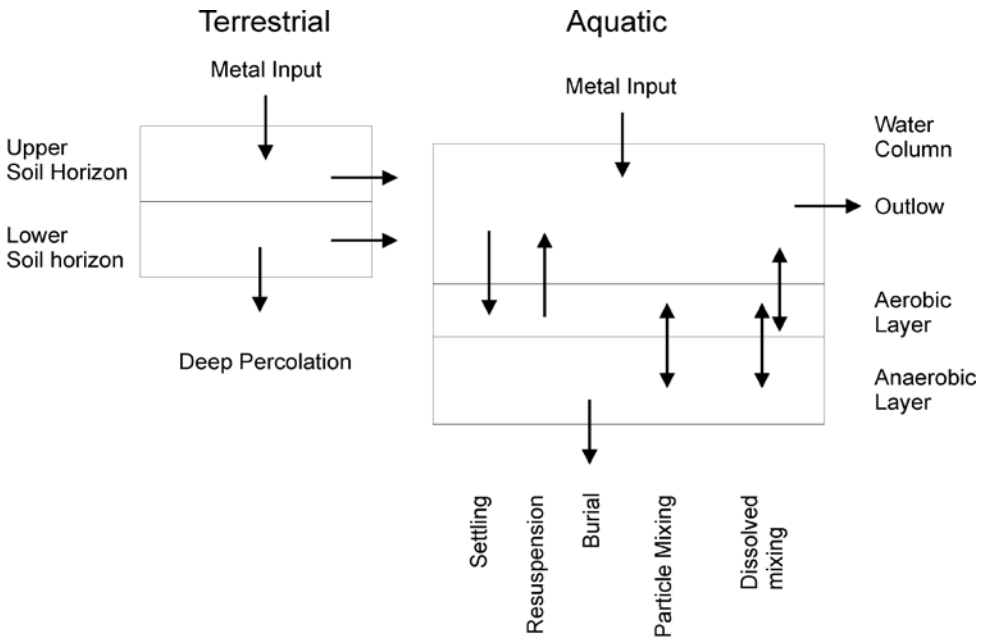

Figure 11. Schematic Representation of the Unit World Model for Metals

Source:

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The soil model comprises two soil horizons, containing solids and solution. The upper horizon receives the metal of interest, in soluble form. The soil solution flows from the upper horizon to the lower, or directly to a surface water. Soil solution from the lower horizon flows to the surface water, or is lost, together with dissolved metal, and metal bound to suspended particulate matter SPM), to deep percolation. The physical and chemical conditions are specified for each horizon; the upper horizon has a higher organic matter content than the lower. The processes governing metals in soils include: solution speciation (described with WHAM6), solid-solution partitioning (described using K_D values, characterised by multiple regression equations with pH and soil organic matter (Sauvé et al. 1998, 2000), and taking into account competition for DOM binding sites by Al and FeIII species (Tipping et al. 2002), and particle ageing (to be characterised for different metals on the basis of experimental information, taking account of soil pH), and the input flux of background metals from weathering. The value of F_{in} (moles m^{-2} a^{-1}) that is sought from the model corresponds to the Critical Load.

There are very few key processes that most significantly influence the outcome of the model (i.e., the critical load). These are the input terms of ecotoxicity and bioaccumulation, the speciation and partitioning reactions between water, sediment, and soil that determine both the fate – the compartments where the metal finally resides – and the bioavailability. Additionally, the transfer of metals into non-bioavailable forms has a significant impact on the critical load. In this model these transfer processes are aging reactions in soils and AVS-binding of the metal. The approach assumes that the soluble metal form is introduced to the air compartment and is distributed appropriately to the soil and water compartments. The calculation of the fraction of soluble metal relative to the parent compound, or “transfer” factor, is done as a separate calculation.

The Unit World Model approach is based on well-established principles governing the environmental behaviour of metals. However, at the present time the proposed approach should be considered as a conceptual framework embodying components that are at different stages of development and evaluation. It will therefore be necessary to undertake a series of well integrated activities to move forward from the conceptual stage to a fully implemented and accepted evaluative method that is capable of tracing the significant fate and transport processes of a wide range of metals and predicting both the concentration and speciation at the exposure point with a sufficient degree of accuracy to reflect the objectives of the assessment, e.g., classification, ranking, or screening level risk assessment.

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