

Framework for Metals Risk Assessment



EPA 120/R-07/001
March, 2007

Framework for Metals Risk Assessment

Office of the Science Advisor
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

LIST OF TABLES	vii
LIST OF FIGURES	vii
LIST OF ABBREVIATIONS AND ACRONYMS	viii
PREFACE	xiii
AUTHORS	xvi
EXECUTIVE SUMMARY	xvii
1. INTRODUCTION	1-1
1.1. PURPOSE AND AUDIENCE	1-1
1.2. METALS FRAMEWORK SCOPE.....	1-3
1.3. METALS ASSESSMENT CONTEXT	1-3
1.3.1. National Ranking and Categorization.....	1-4
1.3.2. National-Level Assessments.....	1-6
1.3.3. Site-Specific Assessments	1-8
1.4. KEY PRINCIPLES TO CONSIDER IN METALS RISK ASSESSMENT	1-9
1.4.1. Metals are Naturally Occurring Constituents in the Environment and Vary in Concentrations Across Geographic Regions	1-9
1.4.2. All Environmental Media have Naturally Occurring Mixtures of Metals and Metals are Often Introduced into the Environment as Mixtures	1-10
1.4.3. Some Metals are Essential for Maintaining Proper Health of Humans, Animals, Plants, and Microorganisms	1-10
1.4.4. The Environmental Chemistry of Metals Strongly Influences Their Fate and Effects on Human and Ecological Receptors.....	1-10
1.4.5. The Toxicokinetics and Toxicodynamics of Metals Depend on the Metal, the Form of the Metal or Metal Compound, and the Organism’s Ability to Regulate and/or Store the Metal	1-11
2. FRAMEWORK FOR METALS RISK ASSESSMENT	2-1
2.1. HUMAN HEALTH AND ECOLOGICAL RISK ASSESSMENT: PLANNING AND PROBLEM FORMULATION	2-1
2.2. METALS CONCEPTUAL MODEL	2-4
2.3. ASSESSMENT PHASE.....	2-10
2.3.1. Bioavailability.....	2-10
2.3.2. Exposure Characterization.....	2-11
2.3.3. Characterization of Effects/Hazard Analysis.....	2-14
2.4. RISK CHARACTERIZATION	2-16
3. ENVIRONMENTAL CHEMISTRY, TRANSPORT AND FATE.....	3-1
3.1. INTRODUCTION AND TERMINOLOGY	3-1
3.1.1. Hard and Soft Acids and Bases: The Stability of Complexes	3-2
3.1.2. Transformations	3-3
3.1.2.1. <i>Biotic Methylation Transformations</i>	3-5
3.1.2.2. <i>Abiotic Transformations</i>	3-6
3.1.3. Aquatic Chemistry	3-7
3.1.3.1. <i>Processes</i>	3-7
3.1.3.2. <i>Speciation and Complexes</i>	3-7

3.1.3.3. <i>Importance of pH and Redox Conditions</i>	3-9
3.1.4. Ground Water and Metals Mobility	3-9
3.1.4.1. <i>Application of Partition Coefficients to Metal Mobility in Ground Water</i>	3-11
3.1.5. Sediment Chemistry	3-13
3.1.5.1. <i>Metal Chemistry in Sediments</i>	3-14
3.1.5.2. <i>Estimating Metal Distribution in Sediments</i>	3-16
3.1.6. Soil Chemistry	3-17
3.1.6.1. <i>Key Parameters Affecting Metal Bioavailability in Soils</i>	3-18
3.1.6.2. <i>Adsorption Behavior of the Metals of Concern</i>	3-19
3.1.6.3. <i>Aging of Metals in Soil</i>	3-19
3.1.6.4. <i>Dissolution and Transformation of Metals</i>	3-20
3.1.6.5. <i>Soil Metal Transfer to Plants</i>	3-20
3.1.7. Atmospheric Behavior/Chemistry	3-21
3.2. METAL FATE AND TRANSPORT	3-23
3.2.1. Aquatic and Terrestrial Transport Pathways for Metals	3-24
3.2.1.1. <i>Aquatic Transport Models</i>	3-26
3.2.2. Terrestrial Fate and Transport	3-29
3.3. ATMOSPHERIC FATE AND TRANSPORT	3-29
4. HUMAN HEALTH RISK ASSESSMENT FOR METALS	4-1
4.1. METALS PRINCIPLES	4-2
4.2. HUMAN EXPOSURE ASSESSMENT	4-3
4.2.1. Background Levels	4-3
4.2.2. Bioavailability	4-4
4.2.3. Susceptible Populations	4-5
4.2.3.1. <i>Life Stage</i>	4-6
4.2.3.2. <i>Demographics</i>	4-6
4.2.3.3. <i>Pregnancy and Lactation</i>	4-6
4.2.3.4. <i>Concurrent Damage or Disease</i>	4-6
4.2.3.5. <i>Nutritional State</i>	4-7
4.2.3.6. <i>Genetic Polymorphisms and Variability</i>	4-7
4.2.4. Environmental Release, Transport, and Fate	4-8
4.2.5. Route-Specific Differences in Effects	4-8
4.2.5.1. <i>Inhalation Exposure</i>	4-8
4.2.5.2. <i>Dietary Exposure</i>	4-10
4.2.5.3. <i>Incidental Soil Exposure</i>	4-11
4.2.5.4. <i>Drinking Water Exposure</i>	4-11
4.2.5.5. <i>Dermal Exposure</i>	4-12
4.2.6. Integrated Exposure	4-12
4.2.6.1. <i>Modeling</i>	4-12
4.2.7. Biomarkers	4-13
4.3. HAZARD CHARACTERIZATION	4-14
4.3.1. Mixtures and Interactions	4-14
4.3.2. Essentiality	4-16
4.3.3. Forms of Metals	4-18
4.3.4. Toxicokinetics/Toxicodynamics	4-18
4.3.4.1. <i>Absorption</i>	4-20
4.3.4.2. <i>Distribution</i>	4-20

4.3.4.3. <i>Metabolism</i>	4-21
4.3.4.4. <i>Excretion</i>	4-21
4.3.4.5. <i>Kinetic Modeling</i>	4-22
4.3.5. Metal Toxicity.....	4-23
4.3.5.1. <i>Noncancer Effects of Metals</i>	4-23
4.3.5.2. <i>Carcinogenic Effects of Metals</i>	4-24
4.3.5.3. <i>Issues Related to Evaluation of Toxicity Tests for Metals</i>	4-25
4.3.6. Dose-Response Assessment.....	4-26
4.4. RISK CHARACTERIZATION	4-27
5. AQUATIC ECOLOGICAL RISK ASSESSMENT FOR METALS.....	5-1
5.1. METALS PRINCIPLES.....	5-1
5.2. CHARACTERIZATION OF EXPOSURE.....	5-2
5.2.1. Background Levels	5-2
5.2.2. Forms of Metals	5-3
5.2.3. Exposure Pathway Analysis.....	5-4
5.2.4. Fate and Transport of Metals	5-5
5.2.5. Toxicokinetics and Toxicodynamics (Bioavailability and Bioaccumulation Issues).....	5-6
5.2.5.1. <i>Aqueous Phase</i>	5-6
5.2.5.2. <i>Sediment Phase</i>	5-8
5.2.5.3. <i>Dietary Phase</i>	5-9
5.2.5.4. <i>Bioaccumulation and Trophic Transfer</i>	5-11
5.3. CHARACTERIZATION OF EFFECTS	5-14
5.3.1. Essentiality.....	5-14
5.3.2. Toxicokinetics/Toxicodynamics (Toxicity Issues).....	5-14
5.3.3. Metal Mixtures.....	5-15
5.3.4. Critical Body Residues	5-17
5.3. RISK CHARACTERIZATION	5-19
6. TERRESTRIAL ECOLOGICAL RISK ASSESSMENT FOR METALS.....	6-1
6.1. METALS PRINCIPLES.....	6-1
6.2. CHARACTERIZATION OF EXPOSURE.....	6-1
6.2.1. Natural Occurrence of Metals.....	6-1
6.2.2. Forms of Metals	6-3
6.2.3. Exposure Routes	6-3
6.2.4. Soil Transport and Fate Models.....	6-3
6.2.5. Toxicokinetics/Toxicodynamics.....	6-4
6.2.5.1. <i>Bioavailability</i>	6-4
6.2.5.2. <i>Bioaccumulation</i>	6-5
6.2.6. Soil Invertebrate Exposure.....	6-6
6.2.7. Plant Exposure	6-7
6.2.8. Wildlife Exposure	6-8
6.3. CHARACTERIZATION OF EFFECTS	6-11
6.3.1. Essentiality.....	6-11
6.3.2. Toxicity Tests	6-13
6.3.3. Metal Mixtures.....	6-14
6.3.4. Critical Body Residues	6-15
6.3.5. Plant and Soil Invertebrate Toxicity	6-16

6.3.6. Wildlife Toxicity.....	6-17
6.4. RISK CHARACTERIZATION	6-18
REFERENCES	R-1
APPENDIX A: FRAMEWORK FOR METALS RISK ASSESSMENT	
CONTRIBUTORS AND REVIEWERS.....	A-1

LIST OF TABLES

Table 3-1. Hard and soft acids (metal cations) and bases (ligands).....	3-3
Table 3-2. Examples of organometallic compounds.....	3-4
Table 3-3. Metals/metalloids involved in methylation processes.....	3-5
Table 3-4. General trends of environmental factors affecting rates of methylation/demethylation	3-6
Table 4-1. Metal essentiality for humans.....	4-17
Table 4-2. Summary of major differences in kinetic behavior of organic compounds compared to metals and inorganic metal compounds in humans	4-19
Table 6-1. Qualitative bioavailability of metal cations in natural soils to plants and soil invertebrates.....	6-8
Table 6-2. Qualitative bioavailability of metal anions in natural soils to plants and soil invertebrates.....	6-8
Table 6-3. Metals classified by their known essentiality	6-13

LIST OF FIGURES

Figure 1-1. Categories of metals assessments under EPA statutory framework	1-5
Figure 2-1. Risk assessment/risk management process for metals.....	2-2
Figure 2-2. Generic conceptual model for metals risk assessment.....	2-6
Figure 2-3. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems	2-12
Figure 3-1. Approximate positions of some natural environments in terms of Eh and pH	3-10
Figure 3-2. A generalized model framework for chemical fate and transport in an aquatic system.....	3-26
Figure 6-1. Generalized representation of 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	6-10

LIST OF ABBREVIATIONS AND ACRONYMS

1CFOK	One-Compartment, First-Order Kinetics model
ABA	Absolute bioavailability
aBLM	Aquatic Biotic Ligand Model
ANZECC	Australian and New Zealand Environment and Conservation Council
ARMCANZ	Agriculture and Resources Management Council of Australia and New Zealand
ATSDR	Agency for Toxic Substances and Disease Registry
AVS	Acid-volatile sulfide
AWQC	Ambient Water Quality Criteria
AWQS	Ambient Water Quality Standards
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BF	Bioaccessible fraction
BLM	Biotic Ligand Model
BSAF	Biota/sediment accumulation factor
CBR	Critical body residue
CCA	Chromated copper arsenate
CEC	Cation exchange capacity
CHESS	Chemical Equilibria in Soils and Solutions
CMAQ	Community Multiscale Air Quality model
DEPM	Dietary Exposure Potential Model
DHHS	U.S. Department of Health and Human Services
DL	Diffuse Layer model
DOC	Dissolved organic carbon
DOM	Dissolved organic matter
EC _x	Effect concentration (for x percent of the study population)
ECOFRAM	Ecological Committee on FIFRA Risk Assessment Methods
Eh	Redox (reduction-oxidation) potential
EqP	Equilibrium partitioning
FDA	Food and Drug Administration
FIAM	Free Ion Activity Model
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FNB	Food and Nutrition Board (NAS)
GI	Gastrointestinal tract
HFO	Hydrous ferric oxide
HLA	Human leukocyte antigens
HSAB	Hard and soft acid and base
ICP-MS	Inductively coupled plasma-mass spectrometry
IEUBK	Integrated Exposure Uptake Biokinetic model
IRIS	Integrated Risk Information System
IUR	Inhalation Risk Unit
K _d	Partition distribution coefficient
K _{ow}	Octanol-water partition coefficient
LC ₅₀	Lethal concentration (for 50 percent of the study population)

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

MAP	Metals Action Plan
MCL	Maximum contaminant level
MPPD	Multipathway Particle Dosimetry Model
NAS	National Academy of Sciences
NASQAN	National Stream Quality Accounting Network
NOM	Natural organic matter
NRC	National Research Council
OM	Organic matter
OSWER	Office of Solid Waste and Emergency Response (EPA)
PBPD	Physiologically based pharmacodynamic
PBPK	Physiologically based pharmacokinetic
PBT	Persistent bioaccumulative toxic
PBTK	Physiologically based toxicokinetic
QSAR	Quantitative structure-activity relationship
RAGS	Risk Assessment Guidance for Superfund
RBA	Relative bioavailability
RDA	Recommended dietary allowance
RDDR	Regional Deposited Dose Ratio
RfC	Reference concentration
RfD	Reference dose
RTC	Report to Congress
SAB	Science Advisory Board
SEM	Simultaneously extracted metals
SHEDS	Stochastic Human Exposure and Dose Simulation model
SPC	Science Policy Council (EPA)
SRWG	Science and Research Working Group (SRWG) of the Non-Ferrous Metals Consultative Forum on Sustainable Development
STORET	Storage and Retrieval data system
TCLP	Toxicity Characteristic Leaching Procedure
TMDL	Total Maximum Daily Load
TRIM	Total Risk Integrated Methodology
TRV	Toxicity reference value
TSCA	Toxic Substances Control Act
U.S. EPA	U.S. Environmental Protection Agency
WER	Water-effect ratio
WHAM	Windermere Humic Aqueous Model
WHO	World Health Organization
WHO/IPCS	World Health Organization/International Programme on Chemical Safety

PREFACE

Many U.S. Environmental Protection Agency (EPA or the Agency) programs are designed to develop guidelines on how to regulate metals. In this process, decisions can range from setting environmental release standards, to establishing protective levels in different environmental media, to setting priorities for programmatic or voluntary efforts. A fundamental input to the decision-making process for most EPA programs is an assessment of the potential risks to human health and the environment.

EPA's Science Policy Council (SPC) recognizes that metals present unique risk assessment issues. The SPC tasked an Agency workgroup, under the auspices of EPA's Risk Assessment Forum, the challenge of devising a Metals Action Plan (MAP) to establish a process for ensuring the consistent application of scientific principles to metals risk assessment. The MAP included brief descriptions of the Agency's current activities on metals, identified critical scientific issues that need addressing, and recommended the development of a metals risk assessment framework. The MAP stated that the Framework should offer general guidance to EPA programs for considering the various properties of metals, such as environmental chemistry, bioavailability, and bioaccumulation.

Because of the scientific complexity of metals-specific risk assessment, the Agency recognized the need to include stakeholders and the public in the Framework development process and to involve experts throughout the Agency. A stepwise process was initiated, beginning with the creation of MAP and continuing with framework development and review. Workshops and peer-review activities were conducted at regular intervals during development of the Framework to ensure that current, accurate science supports the program applications. To gain additional information, the Agency contracted for the development of issue papers on important topics in metals assessment. These activities, along with input from other federal agencies and review by EPA's Science Advisory Board (SAB), provided additional improvements to the Framework drafting process. Additional details on these activities are provided below.

MAP Stakeholder Input. In February 2002, MAP convened a meeting to gather stakeholder input to help EPA formulate the plan for developing the Framework for Metals Risk Assessment. EPA solicited input on organization and content and received comments that were adopted into the document with the greatest practical extent. The meeting report and comments are available on EPA's Web site at

<http://cfpub2.epa.gov/ncea/raf/recordisplay.cfm?deid=51737> and

<http://cfpub2.epa.gov/ncea/raf/recordisplay.cfm?deid=51736>.

Science Advisory Board Review. In September 2002, EPA's SAB reviewed the MAP and provided comments. By this point, MAP had some of the panel's recommendations are

summarized below; the full text of all recommendations is available at <http://www.epa.gov/sab/pdf/ec103001.pdf>.

- The panel agreed that inorganic metals should be assessed differently from organic pollutants in a number of contexts. Metals are elements and, although they do not degrade, they have complex environmental chemistry. Moreover, some metals are essential for living organisms, and metals occur naturally in the environment.
- The panel agreed that chemical speciation, bioavailability, bioaccumulation, and toxicity are key issues in assessing the hazards of metals, with qualifications.
- The panel recommended consideration of stability and environmental residence times, as well as overall environmental chemistry, to determine temporal characteristics of metal hazards.
- The panel recommended greater emphasis on the combined effects of metals, including nutritional and toxicological considerations.

Issue Paper Topics and Science Questions. As part of the development of the Framework, issue papers were developed to discuss key scientific topics pertaining to metals. The issue paper authors were asked to expand on these topics, with focus on decision-making applications, Framework-specific uses, and research needs. The papers, available at <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>, address the following topics and primary questions:

- **Environmental chemistry.** How can environmental chemistry be better incorporated into assessments for inorganic metals?
- **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 and dietary salts, among others?
- **Ecological effects.** What ecological system characteristics promote increased toxicity from metals?

Peer Consultation Workshop. A draft framework was completed in July 2004, and a peer consultation workshop was held from July 27-July 28 to seek input from expert scientists in the metals risk assessment field. Workshop participants were from academia; industry, state, federal, and Canadian agencies; and various EPA program offices. Stakeholder comments were

also received for consideration. Based on comments received at the workshop, the Agency contracted with a few workshop participants to explore several issues and insufficiencies identified in the human health and environmental chemistry discussions. The Framework draft was revised and made available for inter-Agency review.

Inter-Agency Review. Based on comments received, the framework was revised.

SAB Review and Public Comment. The SAB review was conducted in February 2005, and the final draft of the Framework for Metals Risk Assessment document was completed January 25, 2006. The SAB final report is available on the SAB Web site at http://www.epa.gov/sab/pdf/metals_sab-06-002.pdf. The SAB found that the framework covers the main areas of concern to risk assessors, that some technical corrections and additions were needed, and that the document should be restructured and revised to improve the clarity and precision of discussions. Based on these recommendations, the framework was revised to focus on principles and general metals assessment issues rather than tools.

STEERING COMMITTEE AND CONTRIBUTORS¹

CO-CHAIRS

Anne Fairbrother, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Laboratory, Western Ecology Division, Corvallis, OR
Randall Wentsel, U.S. EPA, Office of Research and Development, Washington, DC

STEERING COMMITTEE

Stephen DeVito, U.S. EPA, Office of Environmental Information, Washington, DC
Alexander McBride, U.S. EPA, Office of Solid Waste and Emergency Response, Washington, DC (Retired)
David Mount, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Laboratory, Duluth, MN
Keith Sappington, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC

FORUM STAFF

Gary Bangs, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC
Marilyn Brower, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC
Elizabeth Lee Hofmann, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC
Pamela Noyes, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC
Seema Schappelle, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC
William Wood, U.S. EPA, Office of the Science Advisor, Risk Assessment Forum, Washington, DC

CONTRACTOR SUPPORT FOR FINAL DOCUMENT

Patrick J. Downey, FTN Associates, Inc., Little Rock, AR
Lynne Haber, Toxicology Excellence for Risk Assessment, Cincinnati, OH
Ingeborg Harding-Barlow, Palo Alto, CA
Charles A. Menzie, Menzie-Cura & Associates Inc., Chelmsford, MA
Kent Thornton, FTN Associates, Inc., Little Rock, AR

Metals issue paper authors and peer consultation workshop participants are listed in Appendix A.

¹ Contributors and reviewers are listed in Appendix A.

EXECUTIVE SUMMARY

The Framework for Metals Risk Assessment is a science-based document that addresses the special attributes and behaviors of metals and metal compounds to be considered when assessing their human health and ecological risks. The document describes basic principles to be considered in assessing risks posed by metals and is intended to foster consistency in how these principles are applied across the Agency's programs and regions when conducting these assessments. Although the audience for the Framework is primarily intended to be Agency risk assessors, it will also communicate principles and recommendations for metals risk assessment to the stakeholders and the public. This guidance will be used in conjunction with guidance developed by the programs and regions for use in site-specific risk assessments, criteria derivation, ranking or categorization and other similar Agency activities related to metals.

The purpose of this document is to present key guiding principles based on the unique attributes of metals (as differentiated from organic and organometallic compounds) and to describe how these metals-specific attributes and principles may then be applied in the context of existing EPA risk assessment guidance and practices. While organic compounds, for example, undergo bioaccumulation, there are unique properties, issues, and processes within these principles that assessors need to consider when evaluating metal compounds. Furthermore, the latest scientific data on bioaccumulation do not currently support the use of bioconcentration factors and bioaccumulation factors when applied as generic threshold criteria for the hazard potential of metals.

While the science surrounding the metals risk assessment principles continues to be studied intensively and evolving rapidly, some areas still lack sufficient information for a quantitative assessment to be carried out. Thus, specific approaches may become outdated or may otherwise require modification to reflect the best available science and others may be addressed only qualitatively until additional information becomes available. Regardless, the following principles are more generalized, fundamental properties of metals and should be addressed and incorporated into all inorganic metals risk assessments:

- Metals are naturally occurring constituents in the environment and vary in concentrations across geographic regions.
- All environmental media have naturally occurring mixtures of metals, and metals are often introduced into the environment as mixtures.
- Some metals are essential for maintaining proper health of humans, animals, plants, and microorganisms.
- Metals, unlike organic chemicals, are neither created nor destroyed by biological or chemical processes; although, these processes can transform metals from one species

to another (valence states) and can convert them between inorganic and organic forms.

- The absorption, distribution, transformation, and excretion of a metal within an organism, depends on the metal, the form of the metal or metal compound, and the organism's ability to regulate and/or store the metal.

This Framework document is not a prescriptive guide on how any particular type of assessment should be conducted within an EPA program office. Rather, it is intended to outline key metal principles and how they should be considered in existing human health and ecological risk assessment practices to foster consistency across EPA programs and regions. Chapter 1 identifies the purpose, audience, and scope of the Framework; includes a discussion of typical programmatic or regulatory contexts under which the Agency might undertake a metals risk assessment; and provides an overview of the metals principles. In particular, the context for risk assessment is an important factor in determining the type of analysis appropriate for a particular situation. To provide a context for discussion of the framework principles for metals, EPA has defined three general categories of assessments: national ranking and categorization, national-level assessments, and site-specific assessments. Each type of assessment can vary in level of detail from simple, screening analysis to complex, definitive assessments. Approaches and methodologies may be appropriate for some or all the risk assessment types and may be more or less applicable to screening or complex assessments. Here and elsewhere, the Framework acknowledges that data may not be available to implement all the steps in a metals risk assessment (e.g., lack of information about metal speciation in some environmental media), requiring use of assumptions and a discussion of how such uncertainty influences the risk outcome.

Chapter 2 reviews the human health and ecological risk assessment paradigm and applies the metals principles to each phase of the risk assessment process using assessment questions. The chapter presents a metals conceptual model showing the interrelationship between the metals or metal compounds of interest and the assessment process. Chapter 3 describes how environmental chemistry issues affect the assessment of metals. Chapter 4 describes how the metals principles should be considered when conducting human health risk assessments, and Chapters 5 and 6 describe how the metals principles should be considered in the context of aquatic and terrestrial risk assessments, respectively.

This document discusses scientific issues and scientific approaches. It is intended to foster the consistent application of methods and data to metals risk assessment in consideration of the unique properties of metals. The Agency will be analyzing the science policy implications and developing appropriate policy approaches that are protective of human health and the environment.

The Framework is the result of contributions from a variety of individuals inside and outside the Agency. Their combined expertise and enthusiasm have improved the technical quality of the document and its applicability for various risk assessment activities.

1. INTRODUCTION

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

Metals Principles

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

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

1.1. PURPOSE AND AUDIENCE

The primary purpose of the Framework for Metals Risk Assessment is to identify key principles that should be addressed in any inorganic metals analysis and to provide EPA program

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

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

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

1.2. METALS FRAMEWORK SCOPE

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

Metals and Metalloids of Primary Interest

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

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

1.3. METALS ASSESSMENT CONTEXT

The context for the risk assessment is a major factor in determining the type of analysis appropriate for any particular situation. The Agency conducts a variety of assessments, from

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

1.3.1. National Ranking and Categorization

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

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

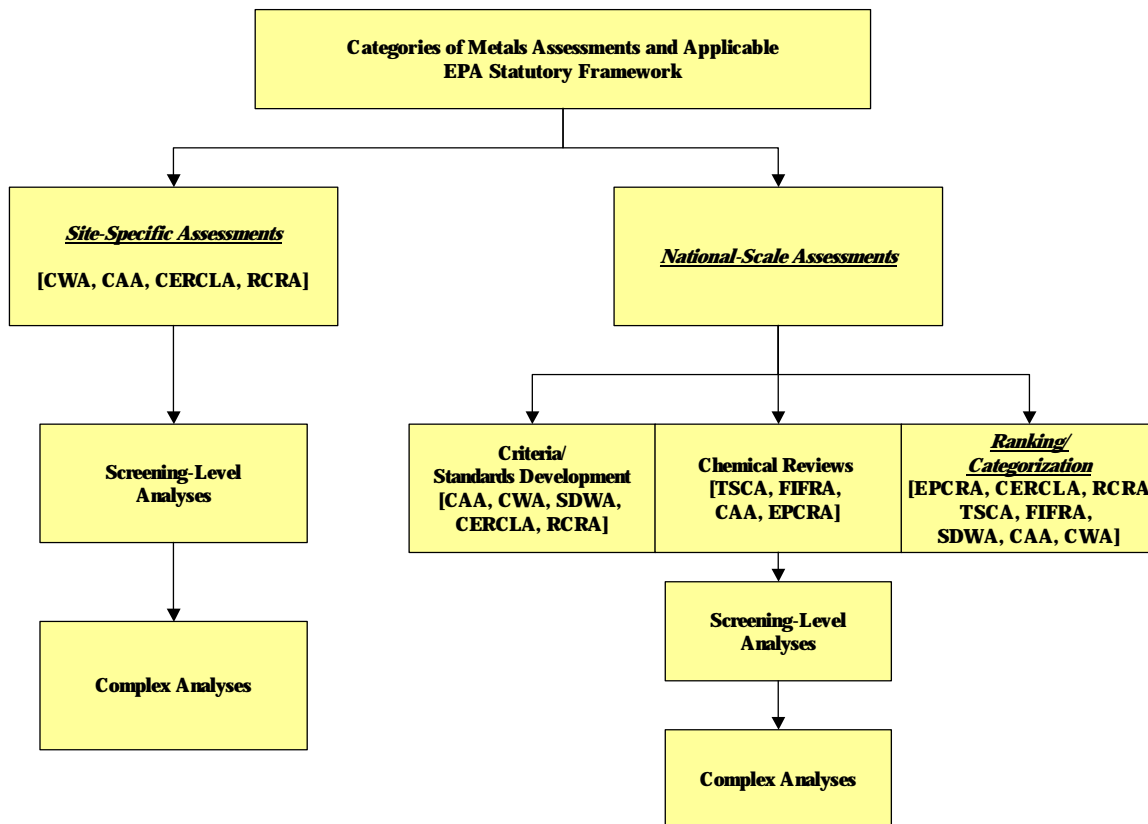


Figure 1-1. Categories of metals assessments under EPA statutory framework.

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

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

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

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

1.3.2. National-Level Assessments

National-level assessments may be performed when the Agency is setting media standards or guidelines for chemicals (e.g., Maximum Contaminant Levels [MCLs], National Ambient Air Quality Standards, AWQC, Superfund soil-screening levels) or when the Agency is using risk assessments to establish controls for environmental releases from industry or other sources (e.g., hazardous waste listings under the Resource Conservation and Recovery Act, residual risk

determinations under the Clean Air Act, and pesticide registrations). These assessments can vary in level of detail from simple, screening analysis to complex, data-intensive definitive assessments. EPA also is charged with establishing controls on environmental releases based on the best available treatment technologies (e.g., maximum achievable control technology for air

Ambient Water Quality Criteria

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

emission and best available treatment technology for surface water discharges and for hazardous wastes). However, even though the standards are based on technological achievability, the Agency typically performs risk assessments in support of these regulations to help inform management decisions and for use in cost/benefit analyses.

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

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

Hazardous Waste Listing Determination

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

1.3.3. Site-Specific Assessments

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

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

Establishing Water Discharge Permit Conditions

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

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

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

1.4. KEY PRINCIPLES TO CONSIDER IN METALS RISK ASSESSMENT

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

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

Implications for risk assessment include the following:

- Humans, other animals, and plants have evolved in the presence of metals and are adapted to various levels of metals. Many animals and plants exhibit geographic distributions that reflect variable requirements for and/or tolerance to certain metals. These regional differences in requirements and tolerances should be kept in mind when conducting toxicity tests, evaluating risks, and extrapolating across regions that differ naturally in metals levels.
- As a result of industrialization, current levels of metals may be elevated relative to levels occurring naturally. Depending on the purpose of the risk assessment, care should be taken to understand and distinguish among naturally occurring levels, current background levels (i.e., natural and anthropogenic sources), and contributions to current levels from specific activities of concern.
- Because the diets of humans and other animals are diverse, there may be wide variability in the dietary intake of some metals (e.g., in seafood), resulting in both temporal variability (e.g., spikes after a seafood meal or with life stage) and geographic or cultural variability.

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

Implications for risk assessment include the following:

- Some metals act additively when they are present together, others act independently of each other, and still others are antagonistic or synergistic. Such interactions are important aspects of assessing exposure and effects.
- Interactions among metals within organisms may occur when they compete for binding locations on specific enzymes or receptors during the processes of absorption, excretion, or sequestration, or at the target site.
- The presence of and amount of other metals are important when conducting and interpreting laboratory tests.

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

Implications for risk assessment include the following:

- Adverse nutritional effects can occur if essential metals are not available in sufficient amounts. Nutritional deficits can be inherently adverse and can increase the vulnerability of humans and other organisms to other stressors, including those associated with other metals.
- Excess amounts of essential metals can result in adverse effects if they overwhelm an organism's homeostatic mechanisms. Such homeostatic controls do not apply at the point of contact between the organism and the environmental exposure.
- Essentiality thus should be viewed as part of the overall dose-response relationship for those metals shown to be essential, and the shape of this relationship can vary among organisms. For a given population, "reference doses" designed to protect from toxicity of excess should not be set below doses identified as essential. Essential doses are typically life-stage and gender specific.

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

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

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

- The form of the metal is influenced by environmental properties, such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides.
- Certain forms of metals are used for evaluating exposure and effects. For example, the free metal ion is used for exposure assessments based on competitive binding of metal to specific sites of action.
- Metals attached to small airborne particles are of primary importance for inhalation exposures, although a few metals and metal compounds may exist as vapors (e.g., mercury).
- Information developed on the fate and effects of one form of a metal may not be directly applicable to other forms.
- Organometallic forms have different characteristics from inorganic metals and metal compounds, and the same general principles and approaches for risk assessment do not apply.

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

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

- Certain metal compounds are known to bioaccumulate in tissues and this bioaccumulation can be related to their toxicity.
- The latest scientific data on bioaccumulation do not currently support the use of bioconcentration factor (BCF) and bioaccumulation factor (BAF) values when applied as generic threshold criteria for the hazard potential of inorganic metals in human and ecological risk assessment (e.g., for classification as a persistent bioaccumulative toxic [PBT] chemical).
- Single value BAF/BCFs hold the most value for site-specific assessments when extrapolation across different exposure conditions is minimized.
- For regional and national assessments, BAF/BCFs should be expressed as a function of media chemistry and metal concentration for particular species (or closely related organisms).
- Trophic transfer can be an important route of exposure for metals, although biomagnification of inorganic forms of metals in food webs is generally not a concern in metals assessments.

- Kinetic-based bioaccumulation models (e.g., DYNBAM) have been shown to accurately describe bioaccumulation resulting from different exposure routes for various metals and aquatic organisms and should be considered as alternatives to the BCF/BAF approach when appropriate data are available.
- Many organisms have developed physiological or anatomical means for regulating and/or storing certain metals up to certain exposure levels such that metals may not be present in organisms in a concentration, form, or place that can result in a toxic effect.
- The organ or tissue in which metal toxicity occurs may differ from the organ or tissue(s) in which the metal bioaccumulates and may be affected by the metal's kinetics. Target organs may differ by species, mainly owing to differences in absorption, distribution, and excretion. Effects at the portal of entry to an organism are less dependent on kinetic processes internal to an organism.
- Both the exposure route and the form of a metal can affect the metal's carcinogenic potential (assessed in the context of human health risk assessment) and its noncancer effects.
- Sensitivity to metals varies with age, sex, pregnancy status, nutritional status, and genetics (due to genetic polymorphisms).

2. FRAMEWORK FOR METALS RISK ASSESSMENT

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

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

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

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

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

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

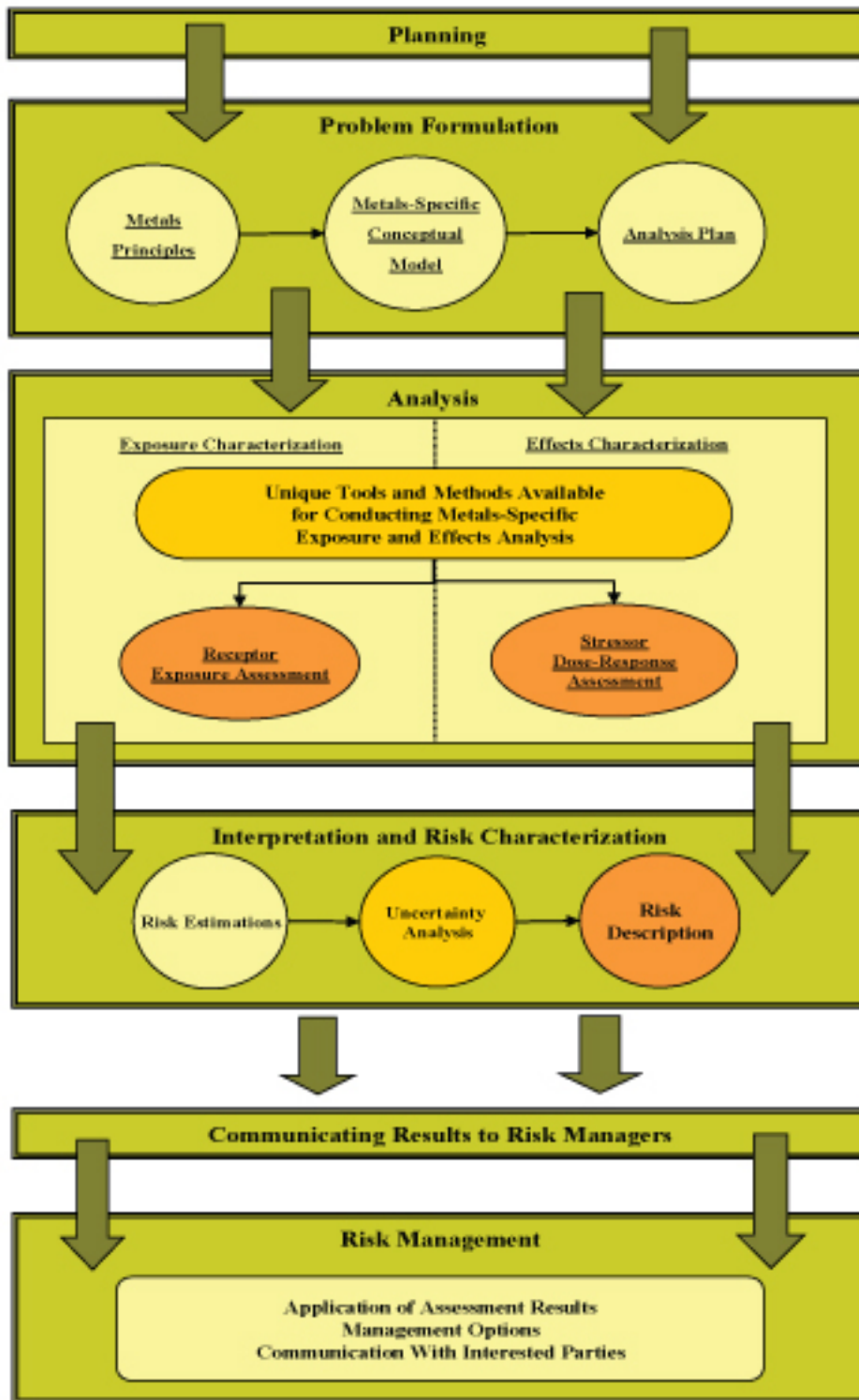


Figure 2-1. Risk assessment/risk management process for metals.

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

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

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

Translating the Metals Assessment Principles into Assessment Questions

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

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

Background Concentrations

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

Mixtures and Interactions

- How will interactions affecting uptake and systemic effects be considered?
- Will issues be considered such as reduction of reactivity and increase in mobility by organic compounds that form complexes with metals and possible increases in toxic effects of organic compounds that form lipophilic complexes with metals?
- Will interactions with other metals and with organics (e.g., As and polycyclic aromatic hydrocarbons) be addressed?

Essentiality

- Are nutritional deficits, which can be inherently adverse and can increase the vulnerability of humans and other organisms to other stressors, be included in the assessment?
- How will both toxicity and deficiencies of essential metals be characterized?

Forms of Metals

- Since environmental chemistry is a primary factor influencing metal speciation and subsequent transport, uptake, and toxicity, how will it be included in the risk assessment?
- How will environmental conditions (e.g., pH and oxidation-reduction reactions) be addressed to determine metal speciation and mobility?

Toxicokinetics/Toxicodynamics of Metals

- What metal-related responses are of most concern in the health risk assessment?
- Which sensitive subpopulations should be considered for each metal of concern?
- How will biotic and abiotic factors that influence the bioavailability and bioaccumulation of metals be incorporated into the risk assessment?
- How will environmental factors that affect metal speciation and metabolic capacity of biota to regulate internal metal concentrations (homeostatic controls) be accounted for when calculating the bioaccumulation potential of metals?

2.2. METALS CONCEPTUAL MODEL

The relationships between the sources, exposure, and effects of metals to human and ecological receptors are complex and often are specific to a particular site, environmental condition, and receptor organism. Because metals are naturally occurring substances that undergo extensive biogeochemical cycling (i.e., are not destroyed but change form), transition functions between environmental loadings, media concentrations, exposed receptors, and the

final organismal or ecosystem responses are affected by natural processes to a much greater extent than those that occur with xenobiotic organic contaminants. The assessor should identify these transition functions in the conceptual model for all metals assessments.

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

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

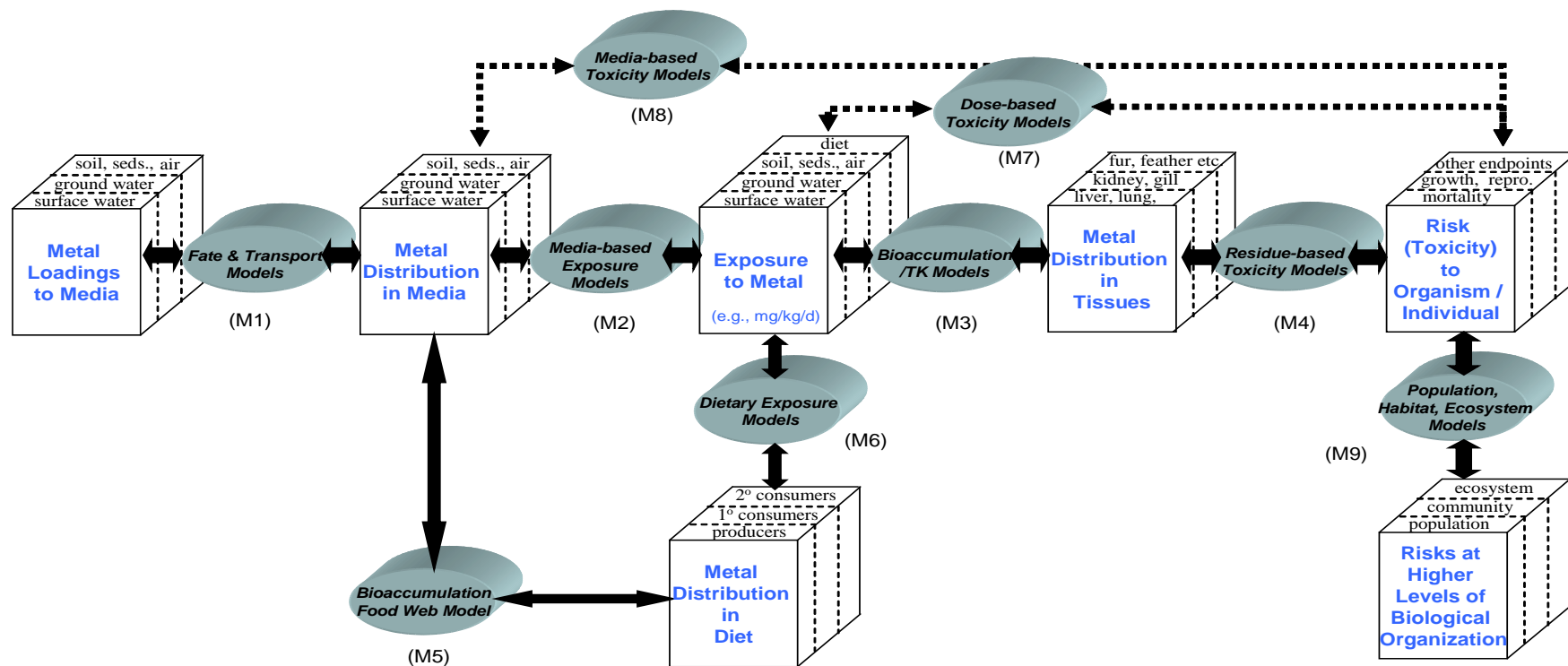


Figure 2-2. Generic conceptual model for metals risk assessment.

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

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

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

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

- **M2: Media-based exposure models.** Media-specific exposure models are mathematical functions used to calculate the exposure of the organism to metals directly from abiotic media (i.e., excluding the food web). Estimating the uptake of metals from environmental media into biota follows many of the same processes used for organic substances, such as understanding dietary preferences, ingestion rates, inhalation rates, and movement patterns. Of particular concern with metals health risk assessments is accounting for the differing bioavailability of metal species to organisms from different environmental media. Exposure to existing environmental levels of metals is another issue of considerable importance in this modeling step. Exposure assessment issues are considered separately for human health, aquatic, and terrestrial receptors (see Chapters 3, 4, and 5, respectively).
- **M3: Bioaccumulation and toxicokinetic (TK) models.** Many organic substances require metabolic activation to become toxic or, conversely, to be detoxified and excreted. Metals do not. Metals may form complexes with proteins or other carrier molecules for distribution to target organs or for sequestration and excretion. Their bioaccumulation is tissue-specific (e.g., cadmium [Cd] in kidneys). The natural occurrence of metals has led to the development of specific mechanisms for uptake, metabolism, distribution/storage, and excretion of metals by organisms. These processes can impact the use and interpretation of bioaccumulation data and the toxicity of bioaccumulated metal.
- **M4: Residue-based toxicity models.** If risk to the organism(s) of concern is to be based on an estimate of internal dose, then information about the relationship of whole-body (or target organ) residue levels to toxic responses should be reviewed by the assessor, either from empirical data or physiologically based toxicokinetic (PBTK) models. Because of the processes discussed in the previous paragraph, this can be particularly challenging for inorganic metals. Metal speciation in the exposure matrix can especially influence this relationship because uptake and organ distribution kinetics are likely to differ. When available, critical body residues (CBRs) can be used to reduce uncertainties in health risk assessments because they account for site-specific bioavailability and multiple exposure pathways. However, CBRs for metals can vary widely depending on exposure pathway (food vs. water), rate of accumulation relative to the detoxification and sequestration processes, and form of bioaccumulated metal. Establishment of a valid residue-response relationship is critical for successful application of CBRs (see Sections 5.3 and 6.3).
- **M5: Bioaccumulation/food web model.** Movement of metals through the food web is complicated by factors of bioaccessibility, bioavailability, essentiality, regulation of metals (uptake and internal distribution), detoxification, and storage as well as accumulation and the natural adaptive capacity of organisms. While the ability to quantitatively address all these factors may be limited at present, the assessor should at least qualitatively address the potential impacts. Bioaccumulation and trophic transfer of metals does occur. However, biomagnification (i.e., increases in concentration through multiple levels of the food web) is rare, with the exception of certain organometallic compounds, such as methyl mercury, that can biomagnify many orders of magnitude in the aquatic food chain. Discussions of methods for estimating bioaccumulation in aquatic and terrestrial food webs are found in Sections 5.2.5.3 and 6.2.5.2, respectively.

- M6: Dietary exposure models.** The assessor must carefully consider the bioavailability of metals from food items in models that estimate dietary exposure to metals. In ecological risk assessments, the wide variation in feeding modes and digestive physiology across species limits the ability to make generalizations with metals. Generalizations require knowledge of dietary preferences, trophic structure of the community, and ingestion and absorption rates. In human health risk assessments, the assessor should consider regional, social, and religious dietary preferences. Although this node of the conceptual model differs very little from risk assessment approaches for organic substances, some metal-specific generalities about the relative importance of exposure pathways can be applied to focus (and simplify) the process. For example, the highest accumulation of metals in plants generally occurs in the roots, and, except for hyperaccumulator species, most plant trophic transfer rates can be assumed to be <1 . Therefore, direct toxicity to herbivores is less likely than for insectivores or from other dietary pathways, and risk to humans from most fruits and vegetables (except roots or green, leafy vegetables) is low. On the other hand, plants are quite sensitive to some metals and may die before achieving levels high enough to be toxic to animals, thereby affecting them indirectly through reduction in food availability. A discussion of dietary exposure assessment issues is found in Sections 5.2 and 6.2 for aquatic and terrestrial ecological receptors, respectively, and in Section 4.2.5.2 for humans.
- M7: Exposure-based toxicity model.** Calculation of an external dose (oral intake, gill binding, etc.) for comparison with toxicity thresholds may depend on information about relative bioavailability (RBA), speciation of the metal or metal salt, dietary preferences and rates, environmental concentrations, essentiality, and metal interactions. Toxicity threshold considerations should be based on comparable information, such as appropriate metal species in exposure media, similarly acclimated or adapted organisms, similar exposure routes, and appropriate combinations of essential metals. Chemical equilibrium models such as MINTEQA2 (Brown and Allison, 1987) may be useful for characterizing the species of metal that is present in particular media, making exposure and effect comparisons more comparable. This forms the basis of the biotic ligand model (BLM) approach (Di Toro et al., 2001; Santore et al., 2001; Paquin et al., 1999) to defining acute aquatic toxicity.
- M8: Media-based toxicity model.** This health risk assessment model compares environmental concentrations with organism response functions without calculating a body burden or internal dose. It is used more frequently for aquatic and soil-dwelling organisms, less frequently for wildlife, and very infrequently for human health assessments. Consideration of RBA, trophic transfer rates, dietary preferences, existing environmental concentrations, and organism adaptations is important for a metals assessment.
- M9: Population, habitat, ecosystem models.** Assessors who carry out Ecological risk assessments often ask questions related to population growth, habitat change, or ecosystem functions in addition to questions related to risks to individual organisms. Most of the models and approaches are similar for both metal and organic substances. However, metals and other inorganic substances are among the fundamental determinants and delimiters of ecoregions (in conjunction with climate, elevation, and

day length associated with latitude). Therefore, knowledge of background levels and the adaptation of organisms to differing metal levels are essential in developing appropriate risk factors for naturally occurring species.

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

2.3. ASSESSMENT PHASE

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

2.3.1. Bioavailability

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

Bioaccessibility, Bioavailability, and Bioaccumulation

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

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

Bioaccumulation of metals is the net accumulation of a metal in the tissue of interest or the whole organism that results from *all environmental exposure media*, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a net mass balance between uptake and elimination of the metal (SAB, 2006).

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

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

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

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

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

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

2.3.2. Exposure Characterization

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

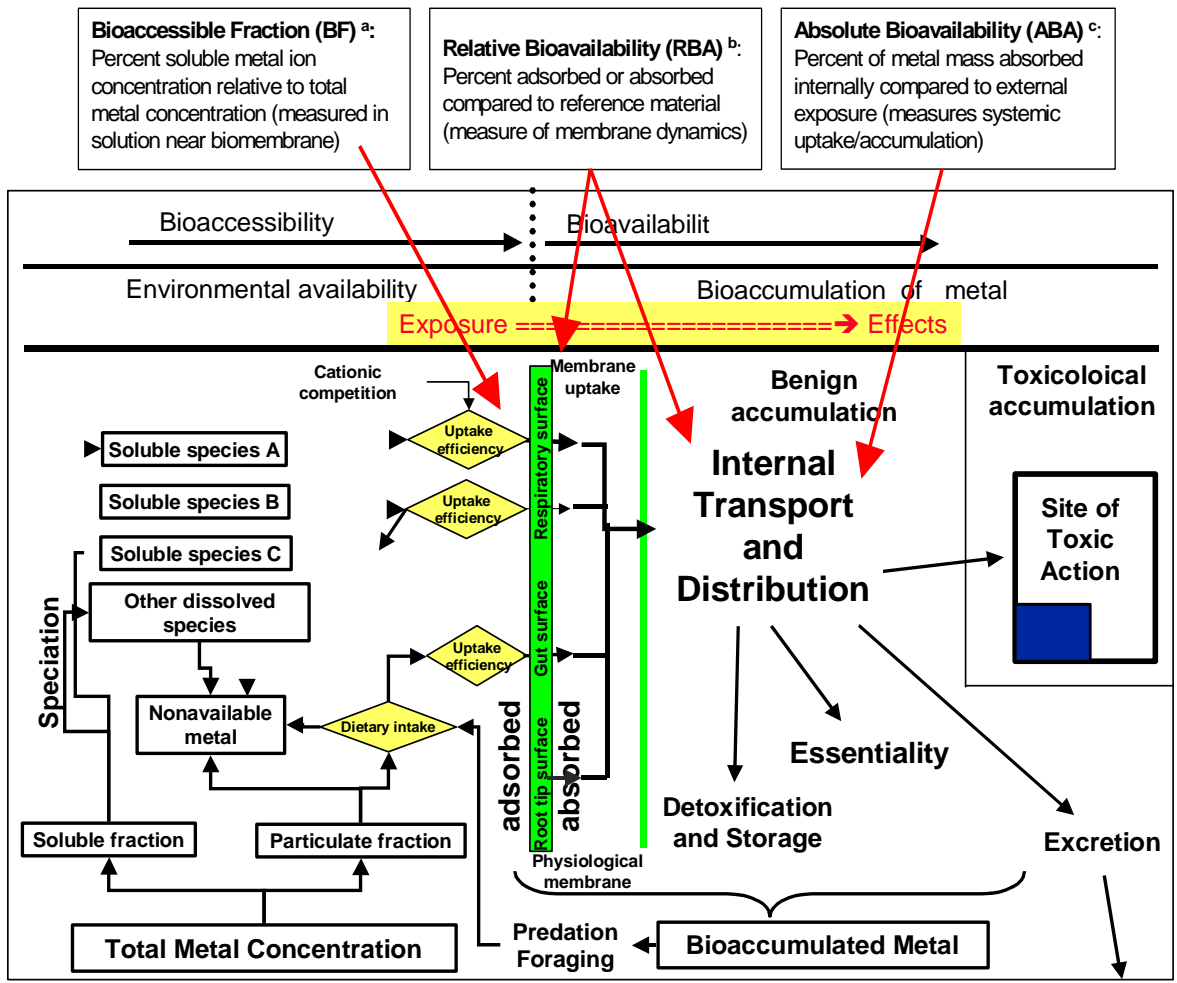


Figure 2-3. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems.

^aBF is most often measured using *in vitro* methods (e.g., artificial stomach), but it should be validated by *in vivo* methods.

^bRBA 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).

^cABA is more difficult to measure and used less in human risk; it is often used in ecological risk when estimating bioaccumulation or trophic transfer.

Source: McGeer et al. (2004).

Background Concentrations

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

Fate and Transport

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

Mixtures and Interactions

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

Essentiality

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

Forms of Metals

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

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

Toxicokinetics/Toxicodynamics of Metals

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

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

2.3.3. Characterization of Effects/Hazard Analysis

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

Background Concentrations

- What is the relationship between environmental (natural and anthropogenic) concentrations and toxicologically relevant metal concentrations?
- For ecological risk assessments, how are acclimation, adaptation, and tolerance issues being addressed in the effects analysis?
- In human health assessments, have concentrations in locally grown or harvested foods been taken into account when estimating elevated metal exposures or estimating relative bioavailability of metals in foods, soil, or water?
- How representative are the toxicity test conditions of the environments being assessed?

Mixtures and Interactions

- Are toxicological effects of metal mixtures being incorporated in the effects assessment? If so, how are they being addressed? If not, what is the rationale for not addressing the toxicity of metal mixtures?
- For particular mixtures of inorganic metals, to what degree are their combined effects additive, antagonistic, or synergistic?
- Is mimicry (competitive interactions among chemically similar metals/metalloids) important in the assessment?
- For site-specific assessments, what evidence exists to indicate the toxicity of the metal(s) of concern is affected by the presence of other metals?

Essentiality

- For essential metals, are nutritional requirements known (e.g., RDA for humans)?
- What is the range between concentrations required nutritionally and those associated with toxicity reference values (e.g., reference concentration [RfC], Ambient Water Quality Criteria [AWQC]) or adverse effect levels used in the risk assessment?
- Are nutritional deficits that can increase the vulnerability of humans and other organisms to other stressors being addressed?

Forms of Metals

- Which forms of the metals are most toxicologically relevant?
- How toxicologically comparable are the forms of metals used in the effects and exposure assessment?
- How might assumptions regarding the toxicity of different metal forms impact the effects assessment? How accurate are these assumptions?

- How will the atmospheric chemistry, transport, and deposition of metals be addressed in the assessment?
- What meteorological factors impact the fate and transport of metals?

Toxicokinetics/Toxicodynamics of Metals

- How does toxicity vary for different metal forms found (or likely to be found) in the assessment?
- Which of these are most important and which are incorporated into the effects assessment?
- How are absorption, distribution, metabolism, and excretion addressed for individual metals or mixtures of concern?

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

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

2.4. RISK CHARACTERIZATION

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

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

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

Background Concentrations

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

Mixtures and Interactions

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

Essentiality

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

Forms of Metals

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

Toxicokinetics/Toxicodynamics of Metals

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

3. ENVIRONMENTAL CHEMISTRY, TRANSPORT AND FATE

3.1. INTRODUCTION AND TERMINOLOGY

A general review of factors pertaining to the chemistry of metals in sediments, soils, waters, and the atmosphere is presented in this chapter in the context of risk assessment. Because the behavior of metals defies simple generalities, understanding the chemistry of the particular metal and the environment of concern is necessary. However, the factors that control metal chemistry and the environmental characteristics used to produce estimates of metal fate and effects can be generalized.

In environmental chemistry, the phase the species occurs in (gas, liquid, aqueous solution, mineral, or adsorbed on an interface between phases) generally is also included in a complete definition. In the context of the environmental chemistry of metals, chemists speak of a metal species as a “specific form of an element defined as to isotopic composition, electronic or oxidation state, complex or molecular structure” and phase (Templeton et al., 2000).

Metal speciation greatly determines the behavior and toxicity of metals in the environment. Speciation refers to the occurrence of a metal in a variety of chemical forms. These forms may include free metal ions, metal complexes dissolved in solution and sorbed on solid surfaces, and metal species that have been coprecipitated in major metal solids or that occur in their own solids. The speciation of a metal affects not only its toxicity but also its volatilization, photolysis, sorption, atmospheric deposition, acid/base equilibria, polymerization, complexation, electron-transfer reactions, solubility and precipitation equilibria, microbial transformations, and diffusivity (Bodek et al., 1988).

The following sections address the application of hard and soft acid and base (HSAB) concepts to metal behavior, including the formation of metal complexes, and the importance of pH and oxidation-reduction reactions to metal mobility. These sections also discuss the occurrence and interactions of the metals of concern in natural media (including surface and ground waters, soils and aquatic sediments, and the atmosphere). Metal sorption behavior, aging in soils, metal dissolution and transformation and transfer to plants, and methods of determining metal speciation in soils and sediments are important topics considered in these sections.

Chemical Species

The International Union of Pure and Applied Chemistry (IUPAC) defines chemical species as chemical compounds that differ in isotopic composition, conformation, oxidation or electronic state, or that in the nature of their complexed or covalently bound substituents, can be regarded as distinct chemical species.

3.1.1. 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 organisms. The 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 concept that helps to explain the strength of metal complexing and metal toxicity is that of HSAB, which was introduced by Pearson (1973). In this concept, metal 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 and the electrons are mobile and easily moved. Soft species prefer to participate in covalent bonding. 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). Hard acids form strong, chiefly ionic bonds with hard bases, whereas soft acids and soft bases form strong, chiefly covalent bonds when they form complexes. In contrast, the bonds formed between hard-soft or soft-hard acids and bases are weak, such that their complexes tend to be rare. Table 3-1 summarizes hard and soft acid and base relationships for the metals of concern.

Hard metals (hard acids), which are the least toxic, preferentially bind with hard bases that contain oxygen, forming weaker bonds with soft nitrogen and sulfur species. The strength of binding between hard metals and hard ligands is usually a function of pH. Many of the hard metals are macronutrients. Soft metals (acids) bind preferentially with soft S and N ligands, forming weaker bonds with hard base species such as hydroxide and sulfate. Soft and borderline metals, and Mn^{2+} , which is hard, form bonds of decreasing strength with soft ligands such as sulfide, generally in the following order: $Pb^{2+} > Cu^{2+} > Cd^{2+} > Co^{2+} \approx Fe^{2+} > Ni^{2+} > Zn^{2+} > Mn^{2+}$. The tendency of metals to bind to soft ligands or to organic substrates (which are

Hard and Soft Acids and Bases

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. Relatively strong 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 soft base and thus bond strongly with soft and borderline soft acid cations.

Ligands

Ligands are simply anions or molecules that form in 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.

Table 3-1. Hard and soft acids (metal cations) and bases (ligands)

Hard acids	Al^{3+} , Ba^{2+} , Be^{2+} , Co^{3+} , Cr^{3+} , Fe^{3+} , Mn^{2+} , Sr^{2+} , U^{4+} , UO_2^{2+} , VO^{2+}
Borderline acids (between hard and soft)	Co^{2+} , Cu^{2+} , Fe^{2+} , Ni^{2+} , Pb^{2+} , Zn^{2+}
Soft acids	Ag^+ , Cd^{2+} , Cu^+ , Hg^{2+} , Hg^+ , CH_3Hg^+ , Tl^{3+} , Tl^+
Hard bases	F^- , H_2O , oxyanions: OH^- , SO_4^{2-} , CO_3^{2-} , HCO_3^- , $\text{C}_2\text{O}_4^{2-}$, CrO_4^{2-} , MoO_4^{2-} , $\text{H}_n\text{PO}_4^{n-3}$, $\text{H}_n\text{AsO}_4^{n-3}$, SeO_4^{2-} , H_2VO_4^- , NH_3 , RNH_2 , N_2H_4 , ROH , RO^- , R_2O , CH_3COO^- , etc.
Borderline bases (between hard and soft)	Cl^- , Br^- , NO_2^- , SO_3^{2-} , $\text{H}_n\text{AsO}_3^{n-3}$, $\text{C}_6\text{H}_5\text{NH}_2$, $\text{C}_5\text{H}_5\text{N}$, N_3^- , N_2
Soft bases	I^- , HS^- , S^{2-} , CN^- , SCN^- , Se^{2-} , $\text{S}_2\text{O}_3^{2-}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{NH}_2$, $\text{R}-$, C_2H_4 , C_6H_6 , RNC , CO , R_3P , $(\text{RO})_3\text{P}$, R_3As , R_2S , RSH , RS^-

“R” refers to an organic molecule.

Source: Adapted from Langmuir (1997); Huheey et al. (1993).

usually soft) is greatest for soft and borderline metals (soft acids), followed by the hard metals (hard acids), typically in the order $\text{Pb}^{2+} > \text{Cu}^{2+} > \text{Cd}^{2+} > \text{Zn}^{2+} > \text{Ca}^{2+} > \text{Mg}^{2+} \gg \text{Na}^+$ (Pickering, 1986).

The tendency of metals to form solid phases, such as sulfides in sediments, is also related to their HSAB qualities. For example, extremely insoluble metal sulfides are formed in anoxic sediments by soft acid metal cations, such as Hg^{2+} ($\log K_{\text{sp}} = -57.25$) or Ag^+ ($\log K_{\text{sp}} = -49.7$), whereas borderline hard and hard metal cations such as Mn^{2+} ($\log K_{\text{sp}} = -19.25$) or Fe^{2+} ($\log K_{\text{sp}} = -22.39$) form slightly more soluble, although still highly insoluble, metal sulfides. Solubility products for all sulfides except Ag_2S are from Di Toro et al. (1990). The product for silver sulfide is from Stumm and Morgan (1970).

3.1.2. Transformations

As discussed previously, metals and metalloids can exist in the environment in several valence forms. They can also exist as organometallic compounds. Organometallic compounds are compounds that have a metal/metalloid-carbon bond. The bonds in organometallic compounds are generally covalent and between soft acid metals and soft ligands. 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, aquatic, and atmospheric phases may be physically, chemically,

or biologically mediated. Table 3-2 lists examples of some commonly occurring, environmentally stable organometallic compounds.

Table 3-2. Examples of organometallic compounds

Metal/metalloid	Organometallic compounds
As	Methylarsenic acid, dimethyl arsenic acid, trimethyl arsine, trimethylarsine oxide
Pb	Tetramethyl/ethyl lead, trimethyl/ethyl lead, dimethyl/ethyl lead
Hg	Methyl mercury, dimethyl mercury
Se	Dimethyl selenide, dimethyl diselenide, seleno-amino acids
Sn	Tributyltin, bis(tributyltin) oxide

As discussed in this section, organometallic methylation and demethylation rates are influenced by both the 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; however, their effect on methylation/demethylation is poorly understood. The dominant variables differ among locations and between seasons, although it is clear that methylation is predominantly a biologically mediated process. Methylation/demethylation rates are strongly influenced by metal/metalloid speciation and bioavailability.

Environmental methyl-metal concentrations reflect the net methylation rather than simple rates of methyl-metal synthesis. Table 3-3 presents metals that are involved in abiotic or biotic methylation/demethylation processes. With the exception of As and Se, the metals in the table form stable complexes with either methyl or ethyl groups. In addition to methyl/ethyl compounds, metals can also be incorporated biochemically into stable organometallic compounds (e.g., As into lipids and Se into amino acids).

Organometallic environmental transformations may affect both the mobility and toxicity of metals. The transformation rates 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, as discussed in this section.

Table 3-3. 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
Biotic demethylation	As, Hg, Sn, Pb

Source: Bodek et al. (1988).

3.1.2.1. 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 the efficiency of methylation is dependent on the activity and structure of the bacterial community. Other bacteria may be involved in methylation. 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 increase.

High temperatures and anaerobic conditions generally favor metal-methylation formation, and demethylation processes are generally favored under low temperatures and/or 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. General trends in methylation/demethylation rates are outlined in Table 3-4.

Table 3-4. 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	↑	↓	?	?	?	?	↓	↑	↓
Methylation 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.

The inhibitory effect of sulfide is probably not due to metal sulfide formation but, rather, to the formation of less bioavailable 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) concentrations, DOC may bind with metals/metalloids, rendering them unavailable and thereby reducing biotic methylation rates.

3.1.2.2. *Abiotic Transformations*

Some organometallic compounds, those with electronegativities greater than 1.7, are stable under environmental conditions. In a few instances, metals can undergo abiotic methylation processes. Carbon-metal bonds with more polar (metal electronegatives <1.7) will undergo hydrolysis (reaction with water). Abiotic chemical methylation can occur by three mechanisms: transmethylation reactions between mercury and tin/lead alkyls, reactions with humic/fulvic substances, and photochemical reactions.

3.1.3. Aquatic Chemistry

Exposure and risks associated with metals in aquatic environments depend on the forms of the metals and on the factors that influence the presence of these forms as well as on the fate and transport of the metals.

3.1.3.1. Processes

A number of factors influence the sorption of metals in aquatic systems. Speciation/complexation is the distribution of a given constituent among its possible chemical forms, including metal complexes, which have differing tendencies to be adsorbed or desorbed; precipitation is the process by which dissolved species exceed the solubility limits of their solids, so that some of the species precipitate from solution; colloid formation can result in metals being sorbed or coprecipitated with colloidal-sized particles; biofixation occurs when biological processes (usually involving microorganisms or plants) result in the binding of metals to solid materials; interactions with natural organic matter can also result in sorption. In addition to these factors, sorption is influenced by changes in pH, oxidation potential, salinity, concentrations of competing ions, the nature of sorbent phases and their surface areas, and surface site densities.

Factors Affecting Sorption of Metals
Speciation/complexation
Precipitation
Colloid formation
Biofixation
Interactions with natural organic matter
Changes in pH
Oxidation potential
Salinity
Competing ions
Nature of sorbent phases
Surface site densities

3.1.3.2. Speciation and Complexes

Metal species dissolved in water may occur as free ions, or aquo-ions, or as complexes. Free metal cations are generally surrounded by coordinating water molecules and so have been termed “aquocations,” although by convention the water molecules are ignored when writing chemical reactions involving metal cations.

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:

$$\Sigma Pb = mPb^{2+} + mPbOH^+ + mPbCO_3^0 + mPbHCO_3^+ + mPbSO_4^0 + mPb(\text{suspended solids})$$

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 below:

$$K_{sp} = (\gamma_{Pb} \cdot m_{Pb^{2+}})(\gamma_{SO_4} \cdot m_{SO_4^{2-}})$$

where the terms γ_{Pb} and γ_{SO_4} 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. This equation shows that for a given total Pb concentration, the greater the amount of Pb that is complexed, the lower the concentration of free Pb ion. This means that as the extent of Pb complexing increases, the total Pb concentration must also increase to reach saturation equilibrium 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 (with the exception of metal hydroxide complexes).

For many metals, the free metal ion is thought to be the primary metal species that causes toxicity to aquatic organisms. This is consistent with the free ion activity model (FIAM), which carries the assumption that the free or aquo-ion is the most biologically active form of the dissolved metal. If this is true, 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 can form metal complexes and so provide alternative binding sites for the metal ion. Metal toxicity also will be affected by other dissolved ions (e.g., Na, Ca) that compete with metals for binding sites on the gills of fish or on the respiratory surfaces of other aquatic organisms. However, it should be noted that many metal complexes (whether bound to organic or inorganic ligands) are reversible, particularly if environmental conditions change (e.g., pH decreases).

3.1.3.3. Importance of pH and Redox Conditions

The pH is probably the single most important variable that influences the behavior of metals in the environment. Thus, metal complexes with sulfate, fluoride, chloride, and phosphate are most stable and important below pH 7, whereas metal carbonate and hydroxide complexes become increasingly more important above pH 6–8.

Also, as discussed in Section 3.1.6, hydrogen ion competes with metal cations for adsorption sites, so that adsorption of metal cations by hydrous ferric oxide (HFO), for example, is low in acid systems but increases with increasing pH. In contrast, oxyanions of As, Mo, Se, and Cr tend to be desorbed from HFO with increasing pH because of competition between the oxyanions and OH⁻ ion for sorption sites. Furthermore, the solubility of most metal-containing minerals is greatest under acid conditions, decreasing with increasing pH. Figure 3-1 shows the locus of measured values of oxidation potential (Eh) and pH in aquatic systems. The principal controls on Eh are atmospheric oxygen and organic matter. High Eh (oxidizing or aerobic) conditions are maintained in the atmosphere and in most surface waters and shallow soils in contact with atmospheric oxygen. The lowest Eh values and reducing or anaerobic conditions are found in water-logged soils and sediments that contain organic matter and in ground waters that contain a few milligrams per liter or more of DOC. Intermediate Eh conditions are found in waters and sediments that are only partially oxidized because of their relative isolation from the atmosphere. Measured Eh values may not agree with Eh values computed from the concentrations of redox-sensitive species. The difference between measured and computed Eh values is discussed at length by Stumm and Morgan (1996) and Langmuir (1997).

3.1.4. Ground Water and Metals Mobility

Site-specific nonorganic metal health risk assessments for EPA programs often are used to predict the rate of movement of metals through soils and their subsequent movement and concentrations in ground water. The primary processes governing the environmental fate and transport of metals in the subsurface are advection, dispersion, matrix diffusion, and retardation (U.S. EPA, 1994b). 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 (Langmuir, 1997; U.S. EPA, 1994b) and may involve or be affected by the following:

- **Sorption** - The attachment of metal species to mineral surfaces or other surfaces.
- **Speciation** - The distribution of a given constituent among its possible chemical forms, including metal complexes, which have differing tendencies to be adsorbed or desorbed.

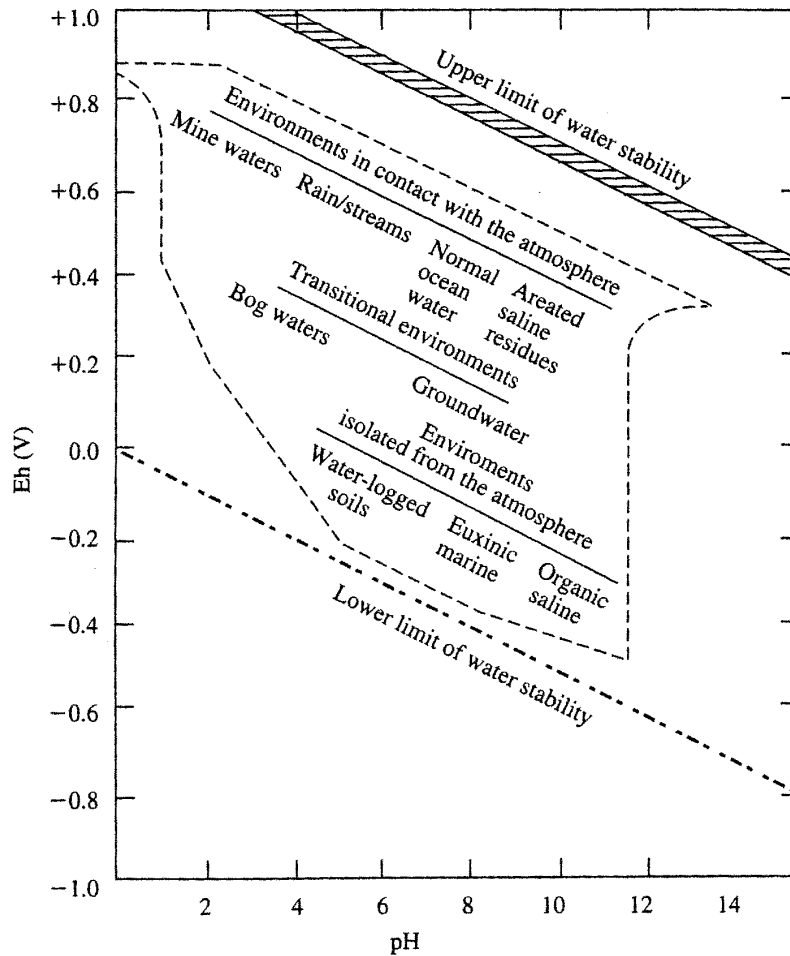


Figure 3-1. Approximate positions of some natural environments in terms of Eh and pH. The dashed line represents the limits of measurements in natural environments.

Source: Baas-Becking et al. (1960).

- **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.
- **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.
- **Biofixation** - The binding of metals to solid materials due to the interactions of microorganisms or plants.
- **Natural organic matter** - (NOM) interactions.

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

3.1.4.1. *Application of Partition Coefficients to Metal Mobility in Ground Water*

Owing 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 = the retardation factor,
 v_p = the velocity of water through a control volume, and
 v_c = the velocity of contaminant through a control volume.

Langmuir (1997) noted that the retardation factor is related to the distribution coefficient through the below 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.

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 HFO, Langmuir (1997) noted that adsorption followed the log equation:

$$\log K_d = -5.48 + 1.77 \text{ pH}$$

The properties and applications of partition or distribution coefficients for metals are comprehensively reviewed in EPA (1999a). These coefficients may be obtained from the literature, estimated using mathematical models, or measured. Properly designed column

experiments generally give results more representative of the *in situ* behavior of soils and sediments than do batch tests (Langmuir, 1997).

Models using partition distribution coefficients (K_d) have significant inaccuracies for metals, and the application of single partition coefficient values for individual metals should be limited to site-specific assessments (when they can be calibrated for a specific site); to regional- and national-scale studies where bounds of potential K_d values are adequate; or reasonably representative single values that have sufficient functionality built in to account for variability due to pH and soil composition.

EPA (1999a) 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/>).

For screening assessments:

- Partition coefficients have been tabulated as a function of pH by EPA (U.S. EPA, 1998b), and the Agency has also presented non-pH-dependent values for Pb (900) (Pb values have large variability and selecting meaningful values is difficult), mercuric chloride (58,000), and Hg (1,000) (U.S. EPA, 1999b).
- In simple systems, the value of $\log K_d$ for metal cation adsorption usually increases linearly with pH, whereas the value of $\log K_d$ generally decreases with pH for anion adsorption.

For definitive assessments:

- It may be possible to estimate metal adsorption with some accuracy without having to measure it in the field, depending on the information available on a specific soil, surface-water, or ground-water system. To do so, at minimum, the risk assessor will need to determine the amounts and surface areas of the potentially sorbing materials (e.g., metal oxides, clays, and organic matter [OM]) in a soil or sediment or in suspension in a stream, and the detailed chemical composition of the water, especially its pH and metal concentration. Literature information can then be used to estimate the sorption properties of these materials for use in the diffuse layer (DL) sorption model.
- If greater accuracy or site specificity is required, it may be necessary to measure metal adsorption in laboratory experiments designed to parameterize the DL model for application to a specific study area. The risk assessor could run experiments (batch tests) that attempt to reproduce the composition of waters and sorbing solids in the study area.

3.1.5. Sediment Chemistry

In addition to the challenges posed by metal chemistry, the sedimentary environment is complex and often highly heterogeneous. Fortunately, generalizations can be made about the sedimentary environment in order to progress toward 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.

Sediment solids can hold up to a million times more metal than an equivalent volume of water. The exact proportion 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. Further, this distribution is dynamic (Diamond and Mudroch, 1990). Because of their large capacity to "hold" metals, sediments have been characterized as "sinks." Sediments can serve as temporary sinks from which 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 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, owing to the ability of Hg to bioaccumulate in its monomethyl form, fish consumption is the critical route of exposure to this metal for humans.²

Many important chemical reactions involving the metals of concern occur in 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

Sediments

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 μm) to silt (2–63 μm) to clay (<2 μm). Because clays have more active binding sites than do the other grain sizes and because of their high surface area-to-volume ratio, clays—or fine-grained particles—are of greatest significance in terms of metal binding.

² 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).

the sediments will reveal decreasing sediment porosity and concentrations of dissolved oxygen because oxygen is consumed as organic matter decomposes. The pH is often relatively constant or may decrease with depth, but alkalinity may increase owing to mineralization of organic matter (Stumm and Morgan, 1996). As dissolved oxygen is consumed, anaerobic microbes use other electron acceptors in redox or oxidation-reduction reactions in the order of nitrate, ferric iron, ammonium, sulfate, and bicarbonate to produce carbon dioxide, ammonia, sulfide, and methane.

The risk assessor can ascertain the redox status of the sediments by measuring the concentration of dissolved oxygen or other redox-sensitive species, by calculating pE (a measure of electron availability 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 redoxcline, which can migrate vertically, depending on the mixing of the overlying water column (e.g., Diamond and Mudroch, 1990). For example, the redoxcline may be 5-10 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.

3.1.5.1. *Metal Chemistry in Sediments*

In this discussion, the risk assessor should consider two pools of metals. The first pool consists of metals that exist as aqueous (or dissolved) species bound to colloids or 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 consists of metals 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, only the exchangeable pool of metals is considered. Note that the exchangeable pool will be composed of naturally occurring metals that are released into solution as a result of weathering and diagenetic processes as well as metals released into the environment as a result of 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 Section 3.1.3, Aquatic Chemistry).

The concentration of metal in the dissolved phase is controlled by sorption to the solid phase. Although 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;

Santschi et al., 1986). If the kinetic limitation of reactions are not considered, the distribution of metals among aqueous species and between the aqueous phase and the solid phase can be estimated by using one of the speciation models. Several speciation/complexation models are available to perform this calculation, such as MINEQL+ (Schecher and McAvoy, 2001), the Windermere Humic Aqueous Model (WHAM) (Lofts and Tipping, 1998), and MINTEQA2 (Allison et al., 1991). These models work well under oxic conditions, but estimates of metal binding are less reliable under anoxic conditions, where metal concentrations are most often controlled by the solubility of metal sulfides. Furthermore, in some circumstances equilibrium may not be achieved, particularly when the redoxcline moves more quickly than the rate of metal reaction or when the reaction is governed by microbial processes, as occurs with the methylation of Hg or As.

In oxic sediment pore waters (above the redoxcline), metals will exist as aqueous species, that is, as freely dissolved ions or metal complexes (e.g., phosphate, sulfate, or carbonate complexes), and associated 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, OM 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 that have been sorbed or coprecipitated with these minerals. Some of the metals released into the pore water may then be adsorbed by iron(III) oxyhydroxides, which are the next to dissolve as the Eh continues to drop. Under reducing conditions, particularly as sulfate is consumed and the S is converted to sulfide, metal concentrations in pore waters again drop as solid-phase metal-sulfides are formed (see discussion below about the role of acid-volatile sulfides [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 redoxcline. The stages in the cycling are, first, the adsorption or coprecipitation of metals with iron and manganese hydroxides under oxidizing conditions; then with the development of moderately reducing conditions, the reduction and dissolution of the manganese and iron oxyhydroxides and consequent release of the associated metals into the water or pore water; followed by their diffusion upward toward the zone of low metal concentrations under oxidizing conditions. It is also possible for dissolved metals to diffuse downward toward the zone of low metal concentration owing to their precipitation as sulfides. 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 reworking rather than the historical record of metal loadings (MacDonald et al., 2000).

The pH controls metal speciation and binding by affecting the species distribution of dissolved ligands (e.g., phosphate, sulfate, carbonate, 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 As, that exist as anionic species.

3.1.5.2. *Estimating Metal Distribution in Sediments*

A main objective in terms of assessing the hazard or risk posed by metals in sediments is estimating the amount of metal that is potentially bioavailable. The bioavailability of metals in sediments is a function of their distribution between the dissolved and solid phases, with dissolved metals in porewater generally considered to be the most bioavailable fraction. 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. (1999, 1997). Although bioavailability is also a function of aqueous phase speciation, limited research has been conducted to estimate metal speciation in pore waters. Generally, for the purpose of ecological risk assessments, the exposure of benthic organisms to sediment-associated metal is assumed to be proportional to the metal concentrations in interstitial water, although some studies indicate that uptake from overlying water (Hare et al., 2003; Roy and Hare, 1999) or ingested sediment may be a significant source of body burdens of metals.

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 using 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., Forstner, 1995; Tessier et al., 1979). However, sequential extraction methods do not cleanly distinguish the occurrence and speciation of different forms of metals in sediments and soils (Tye et al., 2003; Tack and Verloo, 1999). 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 et al. (1993, 1989, 1984; Tessier, 1992) 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, Section 3.1.4 for the theoretical basis for development of partition coefficients).

Speciation/complexation models also may 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. 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 dominant (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. Model estimates are less reliable when other solid-phase substrates are dominant (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.

For anoxic sediments, the availability of sulfide controls metal distribution and solubility. Operationally, AVSs (mainly iron monosulfide) have been considered as a measure of reactive sulfides (Forstner, 1995). Studies have demonstrated an inverse relationship between sediment acute toxicity and AVSs for marine and freshwater sediments (Di Toro et al., 1992, 1990; 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 acute 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 ($AVS > SEM$), which implies sufficient capacity of the AVS to bind essentially all free metal. This topic is further discussed in Section 5.

3.1.6. Soil Chemistry

The cationic metals occur naturally in soils as oxides and hydroxides (Fe, Mn, Al); to a lesser extent they can occur as carbonates, phosphates, and sulfates; and in reducing (usually wet or waterlogged) soils as sulfides, which are highly insoluble. The soil parameters important in affecting sorption and precipitation reactions and the extent of their influence—and thus contaminant bioavailability—depend on the intrinsic properties of the contaminants. In the soil environment, metals can exist as cations (having a positive charge), anions (having a negative charge), or neutral species (having a zero charge). Their form significantly affects their sorption, solubility, and mobility. For example, most soils are chiefly negatively charged; thus, metal cations have a higher propensity to be sorbed by soil particles than do metal anions (U.S. EPA, 2003e).

Cationic metals can react with inorganic soil constituents (e.g., carbonates, sulfates, hydroxides, sulfides), forming aqueous complexes, which may be adsorbed or precipitated in mineral form. Most complexation and precipitation reactions are pH dependent (U.S. EPA, 2003e).

As, Cr, Se, and V complex with O and typically exist as anionic species under most environmentally relevant scenarios (Bohn et al., 1985; Lindsay, 1979). The most common forms of As are arsenate (As(V)) and arsenite (arsenic(III)), which are present in soil solution in the form of AsO_4^{3-} and AsO_3^{3-} , respectively. The chemistry of arsenic resembles that of phosphate (Barber, 1995; Bohn et al., 1985). Cr can exist as chromate (Cr(VI) or CrO_4^{2-}), which is usually considered more soluble, mobile, and bioavailable than the sparingly soluble chromite (Cr(III)), which is normally present in soil as the precipitate $\text{Cr}(\text{OH})_3$ (Barnhart, 1997; James et al., 1997). Similarly, Se can be present as selenates (SeO_4^{2-}) and selenites (SeO_3^{2-}). For V, vanadate (VO_4^{3-}) is the most common form (U.S. EPA, 2003e).

Metals can exist in the pore water as aquo-ions or soluble complexes. The bonding of metal species to soil particles can range from ionic to covalent. For most soils in the United States, negatively charged sites are more plentiful; less than 5% of the total available charge on the soil surface is positively charged. Metals existing as cationic species have a greater propensity to associate with such soils. This makes them less bioavailable, but it also results in greater loading of metals into the soil ecosystem. Anionic metals generally move into pore water—and so are more bioavailable—but leach out of the system much more rapidly. In summary, soil pH and availability of charged sites on soil surfaces are the primary soil factors controlling release of metals to pore water and, subsequently, bioavailability (U.S. EPA, 2003e).

3.1.6.1. 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 soil pH, the availability and character of sorption sites on soil surfaces, the content of Iron and aluminum oxyhydroxides and soil organic matter, and least important, the soil clay mineral content. The following discussion briefly details the key soil parameters affecting the various contaminants availability to the pore water.

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 dissolution and precipitation of metal solid phases, complexation and acid-base reactions of metal species, and metal sorption as well as microbial activity. 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 pore water (Bohn et al., 1985).

3.1.6.2. Adsorption Behavior of the Metals of Concern

3.1.6.2.1. Surface area and surface density. In porous media, the most important sorbent solids for metals are oxyhydroxides of iron and manganese. Their important surface properties are discussed in Langmuir et al. (2003). For a given weight of sorbent, metal sorption capacity is proportional to surface area and surface site density. The greatest surface site densities (positively or negatively charged sites) are those of organic material and the oxyhydroxides. These phases are the strongest and most important sorbents of trace metals. Except for kaolinite, the clays (0.02-2 mmol sites/g) have a surface charge that is largely independent of pH, whereas the surface charge of organic matter and the oxyhydroxides is strongly pH dependent.

3.1.6.2.2. 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 exuded from plant roots and soil microbes (Sumner, 2000). Organic matter is primarily composed of carbon, oxygen, and minor amounts of nitrogen (N) and phosphorus (P). On average, approximately 58% of organic matter is organic carbon. Organic matter in soils ranges 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. The organic acid functional groups typically present in organic matter have a high affinity for metal cations.

3.1.6.3. 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. The aging process is partially reversible if environmental parameters change (e.g., pH decreases), although a portion of the metal ions will be securely entrapped in the soil particle lattice and not available to be resolubilized. It has been well documented that metal chemistry in solutions freshly added or spiked into soils vary from metal forms in field-contaminated soils. Typically, the metal contaminant pool requires time to diffuse into micro- or nanopores and to be absorbed into organic matter and soil particles. These slow reactions are attributed to micropore diffusion, occlusion in solid phases by (co)precipitation and (co)floculation, 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 (Tye et al., 2003; Hamon et al., 1998). 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. After 1 year aging reactions are almost complete and are mostly reversible. At present, information regarding the aging reactions of different

metals and metalloids and sorbing solids, is very limited, so it is not possible to generalize which metal(s) age the fastest or with greater/less reversibility.

3.1.6.4. *Dissolution and Transformation of Metals*

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, the risk assessor should keep in mind 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, the rate of formation of the free ion is not proportional to the dissolution rate of the salt because aging reactions will remove the free ion from the pore water. The risk assessor should consider the relative rates of dissolution and aging simultaneously to accurately predict pore water concentrations.

3.1.6.5. *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) soil solid phases (e.g., iron, aluminum, and manganese 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, Bo, Al, and F, for example, limits residues of these elements in plant shoots. More recently, inductively coupled plasma-mass spectrometry (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 a soil-plant barrier

Several areas for potential errors in the research methodology should be avoided when making these comparisons:

- First, comparison of application rates is valid only after the system has been equilibrated using 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).

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. Pb and Cr are not absorbed by plants to any significant extent at any pH (Chaney and Ryan, 1993). However, each element should 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 Section 3.1.5). For essential elements (e.g., Zn, Cu, Ni), low-solubility species can result in deficiency syndromes. Upon oxidation of the soil, sulfide is quickly oxidized, and the metals are returned to more normal equilibrium reactions of aerobic soils.

3.1.7. Atmospheric Behavior/Chemistry

Most metals and metal compounds exist in the solid phase under normal environmental conditions and thus occur almost exclusively in the particle phase of the atmosphere, where they are ubiquitous. Anthropogenic sources include combustion from fossil fuels and metal industries as well as industrial sources employing specific metal compounds in specific processes. Some airborne metals (e.g., manganese and nickel) may derive largely from crustal sources (U.S. EPA, 1996a). Richardson (2002) included volcanic eruptions and emissions, entrainment of soil and dust, entrainment of sea salt spray, and natural forest fires as significant natural metals emission sources.

For purposes of health risk assessment, particle size is important. The aerodynamic size and associated composition of particles determine their behavior in the human respiratory system. Furthermore, particle size is one of the most important parameters in determining the atmospheric lifetime of particles, which may be a key consideration in assessing inhalation exposures as well as exposures related to exposure pathways involving deposition onto soil or water (U.S. EPA, 1996a). Metals emitted by combustion processes (e.g., the burning of fossil fuels or wastes) generally occur in small particles or fine fraction, which is often characterized by particles less than 2.5 microns in diameter (PM_{2.5}). In contrast, the larger sized, coarse mode particles result from mechanical disruption, such as crushing, grinding, and evaporation of sprays, or suspensions of dust from construction and agricultural operations. Accordingly, metals in coarse mode particles (i.e., those larger than approximately 1–3 μm) are primarily those

of crustal origin, such as Silicon (Si), Al, and Fe (U.S. EPA, 1996a). The *fine* versus *coarse* distinction simply differentiates two relatively distinct size distributions of particles, the separation point of which occurs in the range of 1 to 3 μm . The distinction does not refer directly to particle sampling methods or size fractionations particular to health risk assessment (U.S. EPA, 1996a).

Fine and coarse particles typically exhibit different behavior in the atmosphere; fine mode particles exhibit longer atmosphere lifetimes (i.e., days to weeks) than coarse particles and tend to be more uniformly dispersed across a large geographic region (U.S. EPA, 1996a). Relatively lower dry deposition velocities of fine particles contribute to their persistence and uniformity throughout an air mass (U.S. EPA, 1997c). The larger coarse particles (i.e., greater than 10 μm) tend to rapidly fall out of the air and have atmospheric lifetimes on the order of minutes to hours, depending on their size and other factors (U.S. EPA, 1996a).

In most cases, metals do not undergo transformation while in the particle phase; thus, their removal from the atmosphere is regulated by the rate at which the particles themselves participate in wet and dry deposition processes. For example, metals such as As, Be, Cd, and Pb are generally found in airborne compounds with a single predominate oxidation state (As(III), Be(II), Cd(II), Pb(II)). Some metals (e.g., the transition metals Cr, Mn, and Ni) present the possibility of changing oxidation state *in situ* in the particle, although little is known of these processes (U.S. EPA, 2003d). This is an important consideration for health risk assessment as the different oxidation states also differ in toxicity (such as for Cr).

For metals that can change oxidation states, much of the atmospheric chemistry takes place in the aqueous phase, such as cloud droplets or water films on particles. Metal salts and oxides that dissolve in water can undergo several reversible reactions, including hydration, hydrolysis, polymerization, and reaction with other anions. The equilibrium between these forms depends on the atmospheric conditions, the equilibrium and solubility constants, and the concentrations of other chemicals. Transformations between oxidation states can occur either to increase the oxidation state (such as oxidizing Cr(III) to Cr(VI)) or to reduce it. These oxidation or reduction reactions can occur through reaction with other species, such as dissolved metals, reduced sulfur species, and organic compounds (Seigneur and Constantinou, 1995). Although models exist that can be used to estimate metal speciation in aerosols with liquid water, the reactions are still highly uncertain.

Hg is an exception among the commonly occurring metals; it exists primarily in the vapor phase under most conditions but can also occur in particle and aqueous phases. The risk assessor should consider at least three species of Hg: elemental Hg, which is largely present as a gas; divalent (Hg(II)) inorganic Hg compounds, which are more water soluble; and particulate-phase Hg (Schroeder and Munthe, 1998; U.S. EPA, 1997b). The behavior of Hg in the atmosphere depends strongly on the oxidation state. Elemental Hg is capable of being transported long distances, even globally; divalent Hg deposits within a few hundred kilometers of sources; and

particulate mercury is deposited at intermediate distances, depending on the particle size (Schroeder and Munthe, 1998). Elemental Hg that is deposited can be reemitted from the surface, as can divalent and particulate Hg after biological or chemical reduction to the elemental form.

In the gas phase, elemental Hg can be oxidized to divalent Hg by O₃, OH, H₂O₂, and molecular chlorine (Cl), although other halogen atoms also might be important (Schroeder and Munthe, 1998). In the aqueous phase, elemental Hg can be oxidized by OH, O₃, and dissolved chlorine, and divalent mercury can be reduced by processes such as reaction with HO₂ and S(IV). Both vapor-phase and aqueous atmospheric chemistry may involve multiple phases.

EPA has made a substantial effort to evaluate the atmospheric fate of Hg as a result of the requirements of the Clean Air Act. EPA (1997b) contains a comprehensive evaluation of mercury's atmospheric fate, but this is an area of ongoing research and controversy. EPA continues to actively investigate Hg behavior in the atmosphere (e.g., Landis and Stevens, 2003; Jaffe et al., 2003; Bullock and Brehme, 2002; U.S. EPA, 2001a; Bullock, 2000a, b).

Most sampling and analytical techniques published by EPA for metals in air are oriented toward evaluation of particular-phase total metals rather than metal species (U.S. EPA, 1999a). These methods involve collection of a particular size fraction of particles (e.g., PM_{2.5}, PM₁₀, and total suspended particulates), 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 Hg (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.

Potential for Inhalation

Inhalation of metals is addressed in Section 4.2.5.1. Particle size is likely to be the most important determinant of potential exposure. Particle size also influences the overall fate of metals in the atmosphere.

3.2. METAL FATE AND TRANSPORT

Major metal sources to water and land 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 chloralkali, acid, pigment, electronics, and copper sulfate production.

Some exposure assessments do not involve anthropogenic releases of metals to the environment. Rather, they focus on changes in exposure to environmental metals that result from other aspects of human activities. For example, acidification of freshwater changes Al 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 Se 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).

3.2.1. Aquatic and Terrestrial Transport Pathways for Metals

When an exposure assessment is completed for a site, the available data are usually limited in their coverage with respect to the characterization of exposure levels over both time and space. Depending on the situation, it may be advantageous to use a transport and fate model (i.e., a computational model) to fill in the data gaps, such that an improved characterization of exposure levels is available for use by the risk assessor. Models are also useful in situations where it is desirable to have an estimate of future exposure levels that are expected to result from the implementation of remediation measures. These results can be used to quantitatively evaluate the effectiveness of alternative remediation scenarios that are being considered. The models can also be used to refine the design of the viable alternatives so that the risk assessor can develop an optimal remediation strategy.

Although numerous models are available for use, most are based on the same two fundamental principles: (1) metals are ubiquitous in the environment, as they are found in the aquatic, terrestrial, and atmospheric compartments; (2) within each compartment, they are present in association with water (freely dissolved metal or as organic and inorganic metal complexes), particles (sorbed, precipitated, or incorporated within a mineral phase), and air. The evaluation of metal transport therefore requires evaluation of the distribution of the metal among these phases, within each compartment (air, water, soil), as well as the movement (i.e., the transport) of each of these within and among the various compartments. It is important for the assessor's model to simulate the movement of water and particles explicitly because this provides a way to evaluate differences in the degree to which various chemicals/metals may be transported in association with particles (i.e., via settling and resuspension) or in association with the dissolved phase (diffusive flux of dissolved metal). The analyst represents the environmental setting of interest as a series of discrete, interconnected volumes. Mass balance equations for air, water, solids, and metal are then formulated for each volume to obtain a system of mass balance equations that may then be solved for the concentrations of interest over both time and space. Including all compartments in every model is not necessary. For example, models for a site that is impacted by a smelter might call for use of a model of an atmospheric compartment (e.g., to simulate transport of a release from a stack) and a terrestrial compartment (to simulate fate of

atmospheric inputs to the soil). Alternatively, for an aquatic setting dominated by previously contaminated sediments, it may be sufficient to consider water and sediment transport alone and to neglect the atmospheric and terrestrial compartments.

Although the underlying principles of most models are similar, the included features vary widely from one model to the next. The output from a relatively simple model may be adequate for decision-making purposes in some instances. Some relatively simple models are limited in their applicability to steady-state analyses and spatially uniform conditions, but if this will provide a reasonable and/or conservative representation of conditions at a site, it may provide the analyst with a useful and cost-effective modeling alternative. In other cases, the analysis may require the completion of time-variable simulations to properly represent conditions that vary over time, such as daily or seasonal variations in flow and upstream boundary concentrations, point source loads, and pulse exposures. The analyst should select an appropriate model because not all models will be applicable to every situation. Although, in principle, the more sophisticated models provide the risk assessor with the capability to complete a more detailed and mechanistically based analysis than will a simple model, successful application of these models will require greater resources (data, time, and funding) than will the use of a simpler model. The analyst must also possess a relatively high level of modeling expertise to use the more sophisticated modeling approaches. It is for this reason that the more sophisticated models are usually reserved for use in higher level, definitive assessments.

Many of the models available for use in evaluating the transport and fate of metals were originally developed for application to neutral organic chemicals. As a result, these models frequently include a variety of reactions that are not necessarily relevant to an analysis of metal transport and fate (e.g., biodegradation, photo-oxidation, and volatilization). Although these models still may be of use in an exposure assessment for metals (the nonapplicable processes often may be bypassed), a more significant problem is that they often fail to represent some important metal-specific processes. For example, the evaluation of metal speciation and metal partitioning between dissolved and particulate phases will be represented only in a very simple manner in such models. This limitation may be overcome, at least in part, by performing the requisite metal-specific analyses with a stand-alone chemical equilibrium model, but this approach will place an added burden on the analyst to integrate the results of the two models in a technically defensible manner.

Although models that include some metal-specific capabilities will be discussed as part of this Framework, no single model that is currently available for use includes all the metal-specific features that would be desirable for use. More detailed discussions of these and other transport and fate models, as well as a number of chemical equilibrium models, may be found in Paquin et al. (2003) for aquatic systems and Allen (2002) for terrestrial systems. Additionally, work is in progress to develop updated models that will offer improved metal-specific capabilities (e.g., the

Unit World model (Di Toro et al., 2001). As a result, metal fate and transport models should be viewed as an evolving tool, and new models may be expected in the near future.

3.2.1.1. Aquatic Transport Models

Modeling of metal transport and fate within aquatic systems involves the representation of hydrodynamic transport to simulate movement of water, particulate transport to simulate the movement of particles, and chemical transfers and kinetics to simulate exchange of metal between dissolved and particulate phases and between the water column and benthic sediment (Figure 3-2). The risk assessor has the option of using independent hydrodynamic transport, sediment transport and chemical fate models, or an integrated model that incorporates all these processes.

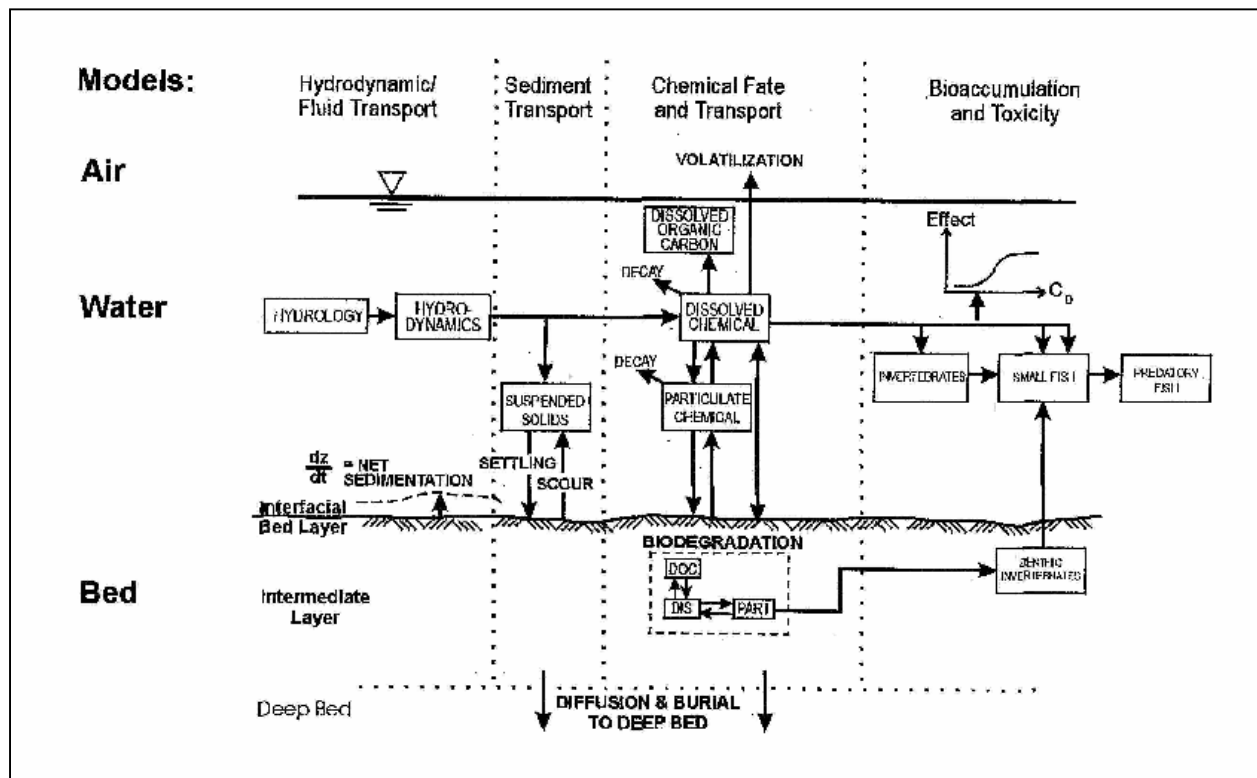


Figure 3-2. A generalized model framework for chemical fate and transport in an aquatic system.

Source: Paquin et al. (2003).

Modeling the movement of metals through an aquatic system begins with a characterization of the water movement through the system. The time scale for the hydrodynamic analysis should be represented in a way that will satisfy the needs of the sediment transport and chemical fate analyses that are also being performed. For example, low-flow

conditions associated with minimum dilution may be judged to be the most critical conditions in a setting involving a point source discharge, while peak flow conditions may need to be simulated in a setting where resuspension of contaminated sediments is the primary concern. A steady-state model might be appropriate for use in the former case, and a time-variable model would likely be needed in the latter case. Thus, the details of the specific problem setting will necessarily have an influence on both model selection and how the model will be used.

Integrated Models

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.

The risk assessor also should be aware of several reviews of fate and transport models that have been completed since the early 1980s. In earlier reviews, Delos et al. (1984) reviewed models for wastewater load allocations, and Mills et al. (1985) described screening-level analyses for water quality assessments of conventional pollutants. The Agency subsequently prepared an updated summary of the features included in the water quality models that were available for use in exposure assessments (U.S. EPA, 1987). Schnoor et al. (1987) simultaneously published their review and included detailed descriptions of fate and transport models and their required input parameters. Later, EPA published a review describing the use of modeling tools for the development of Total Maximum Daily Loads (TMDLs) in watersheds (U.S. EPA, 1997a). More recently, Paquin et al. (2003) completed a review of exposure, bioaccumulation, and toxicity models for aquatic systems, with a focus on their applicability to metals (exclusive of organometallics). Because of the advances that have been made since the mid-1990s with regard to the development of fate and transport models, including some recent efforts to couple these models with metal speciation models and more sophisticated stand-alone hydrodynamic and sediment transport models, the latter reviews by EPA (1997a) and Paquin et al. (2003) tend to include the most up-to-date information with regard to the availability of models that are appropriate for use. These reviews also include example applications of many of the models discussed.

Fate and transport analyses may be performed by using an integrated hydrodynamic, sediment, and chemical transport model or by employing what tend to be relatively sophisticated stand-alone versions of these three submodels. The advantage of the former approach is that integration of the hydrodynamic, sediment, and chemical transport results takes place in a seamless manner with limited need for an assessor's intervention. This is in contrast to the use of stand-alone models, where the output of one model should be formatted in a way that ensures it is amenable to use with the other models that are to be applied. A distinct advantage of the latter approach is that it has the potential to reduce the time needed to complete a model run, an important consideration for a multiyear simulation of a large and complex problem setting. For example, it may not be necessary to repeat the simulation of hydrodynamic and sediment transport if the model input being modified affects only chemical transport (e.g., partition

coefficient). A similar line of reasoning would apply to the use of an integrated transport model that includes metal speciation versus one that uses a stand-alone chemical equilibrium model to satisfy this need.

The partition coefficient, which controls the distribution of metal between the dissolved and particulate phases, is considered to be a key model parameter in chemical/metal fate and transport evaluations (see Section 3.1.4). It is important for several reasons. First, the distribution of metal between the dissolved and particulate phases has a direct impact on the magnitude of particulate fluxes of metal that occur in association with the settling and resuspension of sorbed metal. Second, the partition coefficient also controls the magnitude of diffusive fluxes of metal between the sediment interstitial water and the overlying water column, as this flux is proportional to the concentration gradient of total dissolved metal (free ionic metal + metal-DOC and metal-inorganic ligand complexes) between these compartments. Partitioning reactions also affect the metal bioavailability and the route of exposure to a metal (food vs. water). Given its importance, the risk assessor should recognize that the assumption of equilibrium partitioning is a potential oversimplification in some situations (e.g., near a point source discharge to a receiving water or immediately following a pulse exposure, such as an overflow from a storm sewer system). Under these conditions, the assumption of equilibrium between the dissolved and particulate phases may be less appropriate than is otherwise the case and additional uncertainty will necessarily be associated with the model results. If this situation exists, consideration should be given to conducting special studies (e.g., measurement of free metal concentrations over time in a water sample) to test the validity of the equilibrium assumption.

Analytical Solution Models

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 over metal of time or space.

Modeling of Hg and metalloids, such as As and Se, is complicated by transformation processes that change the form of the metal. Similarly, metals that readily change oxidation state (e.g., Cr) 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, which is focused on inorganic forms of metals. See, for example, the Hg cycling model by Hudson et al. (1994) for further guidance on fate and transport models for Hg. 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). Therefore, all exposure assessments should include an explicit description of model assumptions and associated uncertainties.

3.2.2. Terrestrial Fate and Transport

Movement of metals through soils is dependent on the chemical properties controlling speciation, the presence of ligands that control complexation of metals within pore water (and ground water) and adsorption onto mineral surfaces, and the rate of water flux through the soil. Metals are lost from the soil by leaching into ground water and through metal specific uptake by plants (see Section 3.1.6.5). Sections 3.1.4 and 3.1.6 review 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.

3.3. ATMOSPHERIC FATE AND TRANSPORT

Fine and coarse particles typically exhibit different behavior in the atmosphere: fine mode particles exhibit longer atmospheric lifetimes (i.e., days to weeks) than coarse particles and tend to be more uniformly dispersed across a large geographic region (U.S. EPA, 1996a). Relatively lower dry deposition velocities of fine particles contribute to their persistence and uniformity throughout an air mass (U.S. EPA, 1997c). The larger coarse particles (i.e., greater than 10 μm) tend to rapidly fall out of the air and have atmospheric lifetimes on the order of minutes to hours, depending on their size and other factors (U.S. EPA, 1996a).

In the atmosphere, the behavior of Hg depends strongly on its oxidation state. Elemental Hg is capable of being transported long distances, even globally; divalent Hg deposits within a few hundred kilometers of sources; and particulate Hg is deposited at intermediate distances, depending on the particle size (Schroeder and Munthe, 1998). Elemental Hg that is deposited can be reemitted from the surface, as can divalent and particulate Hg after biological or chemical reduction to the elemental form.

Deposition

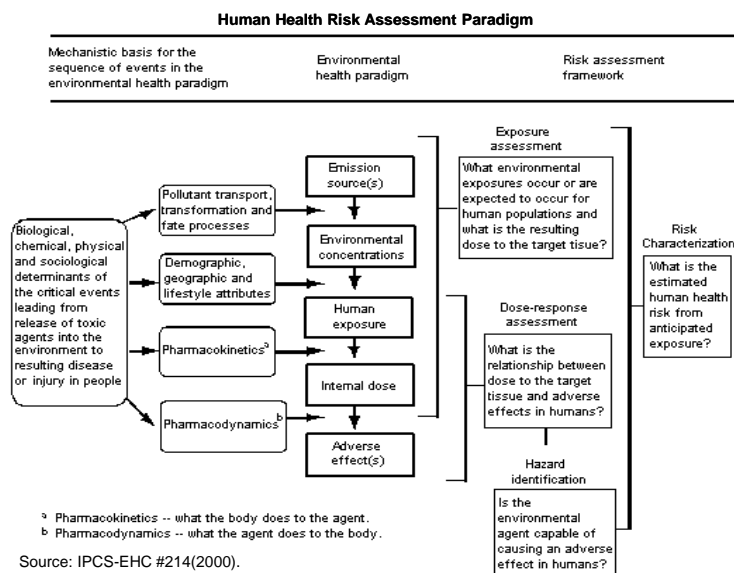
Because most metals occur as particulate matter (hereinafter referred to as *particulates*), their removal from the atmosphere is governed by the rates of wet and dry deposition. These deposition processes represent an important route of exposure for plants, animals, and humans. Some of the deposited metals can come to reside on the surfaces of vegetation, resulting in potential exposure to the plants and to animals that eat the plants. Metals deposited from the atmosphere also come to reside in the leaf litter and uppermost soil surfaces, where they can be a source of exposure for soil organisms, people, and wildlife.

4. HUMAN HEALTH RISK ASSESSMENT FOR METALS

The National Research Council (NAS/NRC, 1996, 1994b, 1983), of the National Academy of Sciences (NAS), described four phases to the human health risk assessment paradigm (Hazard Identification, Dose-response Assessment, Exposure Assessment, and Risk Characterization) and identified risk communication as a fifth area of study. These principles have been further addressed in EPA's *Risk Characterization Handbook* (U.S. EPA, 2000c).

In brief, hazard identification (referred to as "hazard characterization" in recent EPA documents) involves the determination of whether a chemical is or is not causally linked to particular health effects. Dose-response involves the determination of the relationship between the magnitude of exposure and the probability of occurrence of the health effects in question. A parallel step in the process toward the hazard identification and dose-response assessment is exposure assessment. In Exposure Assessment, the risk assessor quantifies the total exposure to a toxic agent in the environment based on amount taken into the body, including any combination of the oral, inhalation, and dermal routes of exposure. For some assessments specific to a single exposure route, exposure may be expressed as an environmental concentration (e.g., ambient air or water concentrations). Depending on the application, the exposure assessment may be specific to a site, a population at a specific location, or it may broadly cover a region or an entire nation. Risk Characterization is the final step in the NAS paradigm. In this phase, the risk assessor summarizes and interprets the information from hazard identification, dose-response, and exposure steps, often by quantitatively comparing exposures with doses that are associated with potential health effects. Risk Characterization addresses the nature and often the magnitude of the human health risks, including attendant uncertainty. These steps are addressed in greater detail in the following sections, with particular attention to the aspects specific to metals.

The information provided here complements that given by the available Agency guidance for the risk assessment process, e.g., for carcinogen risk assessment (U.S. EPA, 2005, 1986), exposure assessment (U.S. EPA, 1992c), developmental toxicity (U.S. EPA, 1991), neurotoxicity (U.S. EPA, 1998c), chemical mixtures (U.S. EPA, 2000b, 1986), and cumulative risk (U.S. EPA,



2003e), and focuses on the unique and specific characteristics of metals and metal compounds that may be applied in metals risk assessments for human health.

4.1. METALS PRINCIPLES

Metals are associated with a variety of health effects that are reviewed in detail in EPA's Integrated Risk Information System (IRIS) Toxicology Reviews, the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, the World Health Organization's International Programme for Chemical Safety (WHO/IPCS) Environmental Health Criteria Documents, and metal toxicology reviews (e.g., Lukaski, 1999; Hathcock, 1996; Mertz, 1995, 1993; Wallach, 1985). Metals have specific attributes that should be considered in all risk assessments. These principles for metals risk assessment (see Chapters 1 and 2) apply in various ways to human health risk assessments, depending on the scale of the assessment (site specific, regional, or national). This section describes applications of the metals principles to human health assessments within the standard risk assessment framework. Specifically, they fall into the risk assessment paradigm as follows:

Background levels	Exposure Assessment
Mixtures	Exposure and Effects Assessment
Essentiality	Effects Assessment
Forms of metals	Exposure Assessment (bioavailability) and
Toxicokinetics/toxicodynamics	Effects Assessment (absorption, distribution, metabolism, and excretion [ADME] and toxicity)

Often times, human health risk assessors start their analysis with a metal-specific reference value (RfD/RfC) and/or cancer potency factor that has been developed through a process separate from the health risk assessment. The role of the human risk assessor is to appropriately integrate the reference values and potency factors with the exposure assessment. Thus, the risk assessor needs an understanding of the toxicological endpoints and mechanisms of action that underlie the derivation of these values to ensure that, for example, the appropriate population and life stages are addressed, appropriate dietary aspects are taken into consideration, and the appropriate exposure pathways are considered. For metals, frequency and duration of exposure, as well as exposure concentrations and metal species, are important parameters for the risk assessor to consider for accurate dose assessments.

4.2. HUMAN EXPOSURE ASSESSMENT

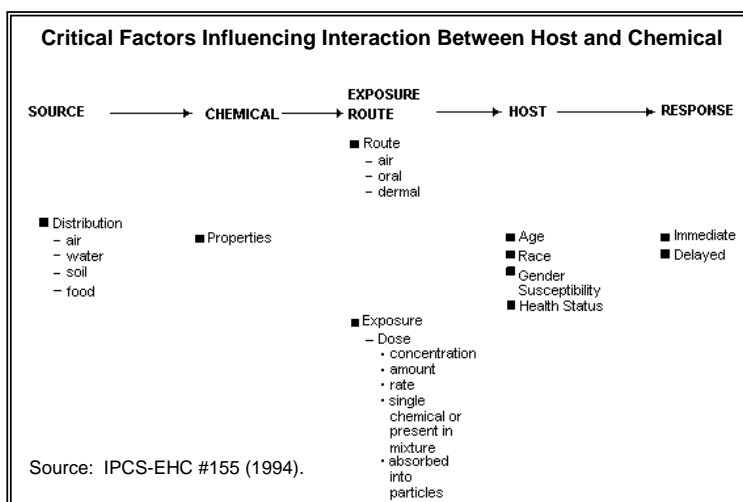
NAS/NRC (1994b) defines exposure assessment as “the determination of the intensity, frequency, and duration of actual or hypothetical exposures of humans to the agent in question. In general, concentrations of the substance can be estimated at various points from its source.” Although there is no specific guidance exclusively for metal exposure assessment, EPA has published guidelines for exposure assessment (U.S. EPA, 1992c), exposure factors (U.S. EPA, 1997e, 1989a), exposure factors for children (U.S. EPA, 2002b), and assessment of early lifestage exposure (U.S. EPA, 2005). Additional reports and principles have been published by the Centers for Disease Control and Prevention (CDC, 2003) and IPCS (2000, 1999, 1994b).

Assessment of human exposures to metals, as with any chemical agent, includes:

- (1) identifying how people come into contact with metals in the environment
- (2) determining the concentrations of specific forms (speciation) of the metal in specific media (e.g., soil, water, air, and biota)
- (3) identifying the pertinent exposure metric (via consideration of dose-response assessment)
- (4) estimating the exposure metric (e.g., oral intake, inhalation exposure concentration, blood concentration), which may involve 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.

4.2.1. Background Levels

Metals are naturally occurring constituents in the environment. As a result of industrialization, current environmental levels of metals can be elevated relative to naturally occurring levels. This may result in a wide variability in the intake of some metals in food (e.g., seafood), drinking water, or air. Strategies for estimating metal concentrations in air, soil, and



Background Metal Concentration

As a result of industrialization, current environmental levels of metals can be elevated relative to naturally occurring levels. Depending on the purpose of the risk assessment, assessors should distinguish among naturally occurring levels, existing background levels, and contributions from specific activities at the local or regional level.

water are discussed in Section 3. In human health risk assessments, the term “background” refers to all existing metal sources except the targeted source. A particular challenge for the risk assessor may be assessing the metal levels associated with the source(s) of interest in light of levels derived from natural and other anthropogenic sources.

4.2.2. Bioavailability

The term “environmentally available fraction” refers to the portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (Lanno, 2003) and represents the total pool of metal at a given time in a system that is potentially able to contact or enter an organism. Of that portion, the bioaccessible fraction (BF) is the amount that actually interacts at the organism’s contact surface and is potentially available for absorption or adsorption (if bioactive upon contact) by the organism. Bioavailability is the extent to which bioaccessible metals (see Section 2.3) cross biological membranes, 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.

The concept of metal bioavailability includes metal species that are bioaccessible and are absorbed or adsorbed (if bioactive upon contact) with the potential for distribution, metabolism, elimination, and bioaccumulation in the organism. 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. The metal salt is influenced by properties of the environment such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides. Depending upon the assessment, it may be appropriate for the risk assessor to consider metal bioavailability and compare the bioavailable fractions used to estimate reference doses (RfDs), or the equivalent, to those measured in the diet, drinking water, or air.

Prediction of toxicity due to exposure to inorganic metals is complicated by wide variations in the bioaccessibility and bioavailability of accumulated metals. The form of the metal (chemical species, compound, matrix, and particle size) influences its bioaccessibility. In turn, the metal form is impacted by properties of the environment such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides. Bioavailability (how much of the ingested metal interacts at the target site) is influenced by nutritional state (deficiency versus excess), age, sex, physiological state, pathological conditions, and interactions with other substances present.

<p style="text-align: center;">Bioavailability/Hazard Relationship</p> <p>If two substances were equally toxic at comparable levels of target organ exposure, the substance with the higher intrinsic bioavailability would pose the greatest risk.</p>
--

It is important that the Exposure Analysis describes the same bioavailable fraction of the metal(s) of concern as that used when estimating the reference value (e.g., the RfD). For

example, measuring total metals in dietary items may include insoluble forms of the metal (particularly if soil contamination is present on the foodstuff), so effective exposure is overestimated. There are both direct and indirect approaches to address the relative bioavailability of metals in the environment: (1) conduct new animal toxicology studies using the metal form encountered in the site assessment; (2) use adjunct scientific data to derive an adjustment to the effective dose identified in the animal study (e.g., data on the distribution of chemical forms of the metal in the environment or at a contaminated site); or (3) use a default assumption that the metal in the environmental samples is the same as that tested. Of the three approaches, the first is more scientifically sound. The second option might be available in some circumstances but is usually precluded by time and financial resource limitations, and the third option, is the most health-conservative.

A fourth alternative conducted for site-specific assessments is for the risk assessor to estimate bioavailability through solubility studies or limited bioavailability studies of specific samples from the site. For example, arsenic bioavailability has been estimated for soils from various contaminated sites (Ng et al., 1998; Freeman et al., 1995, 1993) 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). Additional examples are animal feeding studies with juvenile swine for lead bioavailability adjustments or *in vitro* tests, although the Agency currently requires additional validation of the latter approaches before they can be used as the sole basis for making bioavailability adjustments (U.S. EPA, 2006a).

4.2.3. Susceptible Populations

Risk assessors must specifically consider population subgroups, which may have a greater risk to metals than the general population (U.S. EPA, 2006b). Factors influencing susceptibility to metals include life stage, life style, gender, reproductive status, nutritional state, pre-existing health conditions or disease, and genetic polymorphisms. Children and elderly people do not regulate metal uptake and distribution efficiently and may be at higher risk of accumulating toxic levels (U.S. EPA, 2006b). Pregnant and lactating women have a higher demand for essential elements, and lack of adequate levels of protein in the diet can affect the bioavailability of essential elements (NAS/NRC, 2000). Individuals with chronic liver or kidney disease may have a lower threshold for effects because these are two of the major target organs of metal toxicity. Several well-known, heritable genetic alterations affect people's ability to regulate Cu or Fe, resulting in various deficiency or toxicity problems (WHO/IPCS, 2002). Although many of these same factors are considered in all human health risk assessments, each has attributes specific to metals-associated risks.

4.2.3.1. *Life Stage*

In addition to higher intake per kilogram of body weight (Plunkett et al., 1992), children may also be more sensitive than adults to metal irritants since sensitivity to skin irritants is generally considered to decrease with age. Infants in the immediate postnatal period can also be more susceptible to systemic effects of metals because absorption of essential metals is poorly regulated (WHO, 1996). At the other extreme, older adults are more sensitive to metals that target the kidney (e.g., Cd) because renal function declines with age. Efficiency of intestinal uptake of some trace metals, particularly Zn and Cu, also declines as people age (WHO, 1996; IPCS, 1994).

4.2.3.2. *Demographics*

Differences in lifestyle influence metal exposure. The risk assessor should explicitly investigate different lifestyles of the population of concern. For example, the use of dietary supplements and other consumer products containing essential elements has increased. In addition, folk remedies such as colloidal silver “cure-alls” and folk remedies containing lead tetroxide may contain high levels of metals (McKinney, 1999; Yanez et al., 1994; Pontifex and Garg, 1985; Trotter, 1985; Bose et al., 1983; CDC, 1983, 1982, 1981; Geffner and Sandler, 1980). Smoking provides significant exposure to some metals (e.g., Cd) and can potentiate the effects of exposures from other sources, and excessive alcohol consumption can exacerbate metal effects.

4.2.3.3. *Pregnancy and Lactation*

Pregnancy and lactation increase demand for some essential metals, particularly Cu, Zn, and Fe (NAS/IOM, 2003; Picciano, 1996). Because of physiological changes that include higher Fe and Ca requirements, hormonal changes, and susceptibility to respiratory disease, Zuurbier and Van den Hazel (2005) suggested that pregnant women could be predisposed to the toxic effects of beryllium (Be), Pb, and Mn (2005). Recommended dietary allowances (RDAs) specific to pregnant and lactating women have been developed for a number of essential elements (NAS/NRC, 2000, 2001) and should be considered by risk assessors looking at these metals. Additionally, women lose significant amounts of Fe during menstruation, which may lead to increased absorption and toxicity of Cd (Berglund et al., 1994).

4.2.3.4. *Concurrent Damage or Disease*

In general, people with allergies and those with pre-existing medical conditions have higher-than-average biological sensitivity to *environmental stressors*. For example, diseases or treatments that damage the kidney or liver may increase sensitivity to metals that target these organs. Damage to the lung from smoking can potentiate effects of simultaneously or

subsequently inhaled metals, particularly those that act directly on the lung (e.g., Be, Cd, Cr, and Ni). Skin abrasions or other irritations also can alter exposures to and subsequent effects of metals (although dermal absorption is not a primary route of metals exposure for intact skin).

4.2.3.5. *Nutritional State*

Risk assessors should be aware that dietary differences can affect the absorption of metals, thus changing internal target dose. For example, lack of protein (or the type of protein) can decrease metal uptake, thus reducing potential risk. However, relatively little is known about this risk factor and nutritional state is an area for further study.

4.2.3.6. *Genetic Polymorphisms and Variability*

Risk assessors should be aware of several well-known, heritable, genetic polymorphisms that affect susceptibility to metals. The best known of these are two disorders that affect Cu metabolism: Wilson's disease and Menkes syndrome. Wilson's disease is an autosomal recessive abnormality (prevalence of 1 in 30,000) that causes impaired biliary excretion of Cu, resulting in accumulation in and damage to various tissues, particularly the liver, brain, kidney, and cornea; hemolytic anemia also can result. Menkes syndrome is an X-linked recessive disorder of Cu metabolism (prevalence of 1 in 200,000) that resembles Cu deficiency regardless of level of Cu intake (WHO/IPCS, 2002).

Hemochromatosis is another common inherited disorder. It is characterized by excessive Fe absorption, elevated plasma Fe concentration, and altered distribution of Fe stores (altered iron kinetics). One long-term effect is liver cirrhosis, with increased risk of liver cancer (NAS/IOM, 2003). Another Fe-related genetic polymorphism affecting Pb metabolizing enzymes is delta-aminolevulinic acid dehydratase (ALAD), which has been found to affect the relationship of bone Pb to the cumulative blood index, suggesting that the transfer of Pb from blood to bone is altered. It is suspected that genetic polymorphisms also exist for As metabolism (NAS/NRC, 2001), but these have not yet been defined.

Risk assessors should consider the possibility of genetic differences when assessing potential sensitization reactions. Chronic beryllium disease (CBD) is an immune response, with sensitivity determined by major histocompatibility (MHC) class II genes (U.S. EPA, 1998d). Similarly, sensitivity to Ni is related to the genotype of human leukocyte antigens (HLA)³ (ATSDR, 2003).

³ The major histocompatibility complex is a group of genes on chromosome 6 that code for the antigens that determine tissue and blood compatibility. In humans, histocompatibility antigens are called human leukocyte antigens because they were originally discovered in large numbers on lymphocytes. There are thousands of combinations of HLA antigens.

4.2.4. Environmental Release, Transport, and Fate

The exposure component of a human health risk assessment includes source characterization and analysis of fate and transport of the chemical of interest through environmental media. Models for transport and fate of metals from emission points to environmental receptors of importance to humans (e.g., soils, plants, or animals used in food and fiber) are covered elsewhere in this Framework document (see Section 3.2), as they are similar for both human health and ecological risk assessments. It is recommended the risk assessor conduct this portion of the assessment simultaneously for both human health and ecological assessments to ensure appropriate integration of the results. Human activities that affect the contact time of people with contaminated media also influence the route(s) and total amount of exposure.

4.2.5. Route-Specific Differences in Effects

Risk assessors should consider how route of exposure affects metal bioavailability and whether effects will occur at portal-of-entry or will be due to systemic, target-organ responses. Interactions among metals or other exogenous or endogenous compounds also can affect bioaccessibility of metals and are route dependent. Thus, many metal exposure issues are specific to the route of entry and will be discussed separately in the following sections.

4.2.5.1. *Inhalation Exposure*

Most airborne metals, with a few important exceptions (e.g., Hg and arsine) occur in particulate form. This necessitates certain considerations for inhalation exposure assessment, e.g., how particle size affects respirability (i.e., how much of the pollutant enters the respiratory system). Additionally, inhalation dosimetry for particles involves some distinctly different processes than for gases (i.e., deposition, clearance, dissolution, etc.), which are also influenced by particle size (U.S. EPA, 2004, 1997c). Particle size is thus an important factor in assessing metals exposure, with the focus generally being on particles less than or equal to 10 microns (μ) in diameter (PM₁₀). Larger particles usually do not penetrate far into the respiratory tract and can be cleared to the ingestion route and swallowed. Larger particles may have a larger role as an irritant, affecting a person's eyes and nasal passages, and, if deposited in the uppermost reaches of the respiratory tract, may be transferred to the digestion tract. Thus, for exposure assessments involving measurements (e.g., using area or personal samples), the particle size is an important factor in determining inhalation exposure to metals.

Since inhalation is a primary route of exposure for metals, the risk assessor should have a good understanding of inhalation dosimetry methods and how inputs vary for metals. Key methods for inhalation dosimetry are described in EPA guidance documents (U.S. EPA, 2004, 1997c) and a number of models are available for calculating relative regional respiratory tract

deposition in rodents and humans (reviewed in U.S. EPA, 2004). The guidelines for reference concentration (RfC) development (U.S. EPA, 1990) cite the regional deposited dose ratio (RDDR) model, which has been used for development of a number of RfCs for metals. The multipathway particle dosimetry model (MPPD) developed by the Chemical Industry Institute for Toxicology (CIIT) and the Dutch National Institute of Public Health and the Environment (RIVM) was used in EPA's *Air Quality Criteria for Particulate Matter* (U.S. EPA, 2004). MPPD improves lung dose estimations by considering life-stage-specific parameters, particle clearance from the lung, and differences in oronasal breathing patterns with work load. The human equivalent concentration (HEC) is the concentration that is believed to result in the same dose to the respiratory tract region of interest as was received by the experimental animal species.

In developing inhalation exposure estimates, the risk assessor should pay careful attention to the form of the metal pertinent to the dose-response assessment (e.g., RfC, IUR). Simply measuring the total amount of a metal without regard to speciation may introduce uncertainties into inhalation exposure estimates or other exposure routes. Metal speciation affects a range of processes that change how the metal is deposited in the respiratory tract and subsequently distributed throughout the body and, consequently, its potential toxicity (Bailey and Roy, 1994; Oberdorster, 1992). For example, in assessing the risk of inhaled Cr, the assessor should consider speciation (e.g., Cr⁺³ vs. Cr⁺⁶), as the dose-response assessment includes that specification. The bioavailability of metals via inhalation can be much higher than that of other intake routes. 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 Cd (e.g., Friis et al., 1998; Ellis et al., 1979). Variations in airway structure and respiratory conditions (e.g., as with age) may alter the deposition pattern of inhaled particles and contribute to variations in bioavailability (James, 1994; Xu and Yu, 1986; Phalen et al., 1985). For more information on the consideration of particle size in the dose-response assessment for RfCs and IURs, the risk assessor should refer to U.S. EPA, 1990. For metals having alternative Agency-developed dose-response metrics (e.g., blood Pb concentration), respirability, deposition, and clearance as well as absorption into the circulatory system may need to be addressed as part of the Exposure Assessment.

Risk assessors should be aware of emerging issues in inhalation dosimetry that may have important impacts on exposure assessments for metals (U.S. EPA, 2005). The developing literature suggests that current dosimetry models and traditional dose measures (such as concentration in mass/unit volume) may not adequately characterize human health risk to very small particles, such as particles $\leq 2.5 \mu\text{m}$ (PM_{2.5}) or $< 1 \mu\text{m}$ in diameter (nanoparticles). Much of the recent work on nanoparticle deposition has been conducted with metal oxide particles (e.g., titanium dioxide), and a growing body of literature is becoming available to the risk assessor. The bioavailability of Pb and other metals appears to increase with decreasing particle size,

particularly from the inhalation and oral routes of exposure, so risk assessors should be aware of the potential implications for bioavailability of metal nanoparticles.

Risk assessors should also consider exposure to metals in shower water, in which aerosolization can occur from the hot water tap. Though the magnitude of exposure from showering is unknown and comparable models do not exist for aerosolized metals (Wilkes, 1998), models have been developed to predict human inhalation exposures due to volatile organics from showering (e.g., Guo, 2002; Moya et al., 1999; McKone, 1987). Where appropriate, the risk assessor should address such inhalation exposures during the Risk Characterization phase.

4.2.5.2. Dietary Exposure

Risk assessors should be aware that dietary pathways represent a major exposure route for metals (Choudhury et al., 2001). Estimation of intakes of metals occurring in food requires information on the levels of metals in food and the amount of food consumed (NAS/IOM, 2003). A number of references provide assessors with

national-scale information on dietary exposure to metals (Capar and Cunningham, 2000; Schoof et al., 1999a, b; Thomas et al., 1999; Bolger et al., 1996; Dabeka and McKenzie, 1995; Gunderson 1995; Tsuda et al., 1995; Dabeka et al., 1993). Although large-scale surveys of the metal contents of foods and food consumption patterns have been conducted (e.g., Egan et al., 2002; Ryan et al., 2001; U.S. FDA, 2001; O'Rourke et al., 1999; Thomas et al., 1999; U.S. DHHS, 1996), assessors should be aware that these surveys have several limitations for applications to human health risk assessment. Analysis is often conducted with "market basket" samples of packaged processed foods. With a few exceptions, such applications have not been empirically evaluated against biomarkers of exposure (Clayton et al., 2002, 1999; Choudhury et al., 2001). Risk assessors should be mindful that food consumption surveys are generally limited to short-term consumption (e.g., 1-3 days) and do not capture intra-individual variability that would affect long-term averages. Furthermore, dietary patterns may change over time (e.g., consumption of ethnic foods in childhood may change later), and, thus, patterns discerned at any given time may not accurately represent historical or future exposures. An additional challenge facing the risk assessor is integration of data from separate metal residue and food consumption surveys (e.g., Tomerlin et al., 1997). This leads to considerable uncertainty in estimates of metal exposure via the dietary route.

Dietary Exposure

Due to the diversity of the human diet, there may be wide variability in the intake of some metals in food (e.g., seafood), resulting in both temporal variability (e.g., spikes after a seafood meal) and geographic or cultural variability.

4.2.5.3. *Incidental Soil Exposure*

Infants and children can have enhanced exposures to metals through the pathway of surface dust because (1) they crawl and play in close proximity to surface dust and (2) they often mouth their hands (e.g., finger sucking) and objects in their environment. This causes an intake of surface dust that is generally greater than that which is normally found in adults (e.g., Barnes, 1990). On the other hand, infants have a large salivary response (i.e., they drool and spit up frequently), which may act to reduce overall dust intake. However, risk assessors should be aware that data are limited with regard to distinguishing 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 environments (U.S. EPA, 1994a). Exposure assessment methods for direct soil ingestion are described in the Risk Assessment Guidance for Superfund (RAGS) (<http://www.epa.gov/superfund/programs/risk/ragsa/index.htm>). Additional guidance with respect to children (e.g., amount of soil a child may ingest) can be found in the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002b). Few studies of soil ingestion in adults have been conducted; however, the estimates support the 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). Because concentrations of the metal contaminants in soil can be expected to vary with depth, risk assessors should consider soil metal concentrations at the depth appropriate to the metal(s) of concern as well as human behaviors and activities.

4.2.5.4. *Drinking Water Exposure*

Treatment of surface and/or ground water for human consumption removes dissolved organic carbon and suspended organic sediments that can form complexes with metals (AWWA, 1999). Thus, inorganic forms of metals in treated drinking water will often 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).

Risk assessors estimating the intake of metals in drinking water will require information about concentrations of metals in the water and the amount of water consumed. Data on the metal content of tap water can be obtained from EPA's Office of Drinking Water. EPA's *Exposure Factors Handbook* contains exposure information on daily drinking water ingestion and incidental ingestion of water during swimming and showering (U.S. EPA, 1997e).

Generally, water metal concentrations are measured at the distribution point for municipal water delivery systems. Distribution systems within homes (pipes, storage containers, etc.) can contribute significant amounts of metals (e.g., Pb, Cu) to the home drinking water

(Graziano et al., 1996); consequently, the contribution of metals from home-based pipes, etc., is a source of uncertainty in the human health risk assessment.

4.2.5.5. *Dermal Exposure*

Metals absorption through the skin is limited because the dermal route of exposure is of less concern during a health risk assessment. However, some metals (e.g., Ni and Cr) have the potential to induce toxic and sensitization effects directly on the skin (U.S. EPA, 2001, 1992). Dermal exposure can also lead to intakes via other routes, such as oral exposure via hand-to-mouth transfer or ocular contact.

Potential sources of dermal uptake that the risk assessor should consider include small particles in contact with the skin; metal exposure during bathing, showering, and swimming (NAS/NRC, 2002); and the uptake of metals through damaged skin (e.g., irritated skin, sunburn). Dermal contact with metals in soil also represents a potential route of exposure, but the relatively low lipid solubility of most metals limits absorption through the skin (Paustenbach, 2000; Hostynek et al., 1998). Few studies have actually attempted to quantify the extent or kinetics of the dermal penetration of metals deposited on the skin, and the applicability of these studies to metal species and complexes that occur in surface dust or soil is highly uncertain.

4.2.6. Integrated Exposure

Approaches to integrating exposure across pathways and physiological routes of uptake include modeling, estimates of relative bioavailability, and the use of biomarkers.

4.2.6.1. *Modeling*

Risk assessors have access to only a few specific, integrated exposure models for metals. The Integrated Exposure Uptake Biokinetic (IEUBK) model for Pb in children (U.S. EPA, 1994a; White et al., 1998) was specifically developed for translating exposure measurements into risk estimates. The IEUBK model and background documentation are available on line at: <http://www.epa.gov/superfund/lead/products.htm>.

Risk assessors should not apply this model to other metals because it was derived using Pb-specific information and consequently is pertinent only to Pb. A multipathway exposure model specific for As has also been developed (Cohen et al., 1998). Less complex models linking adult exposures and blood Pb concentrations are available (Carlisle, 2000; Stern, 1996, 1994; U.S. EPA, 1996b; Bowers et al., 1994; Carlisle and Wade, 1992), and a stochastic human exposure model for Pb that is linked to a lead pharmacokinetics model may also be of use to the risk assessor (Beck et al., 2001; O'Flaherty, 1995).

Other models available to risk assessors are EPA's Total Risk Assessment Methodology (TRIM), which is being developed for multipathway risk assessment for air pollutants including

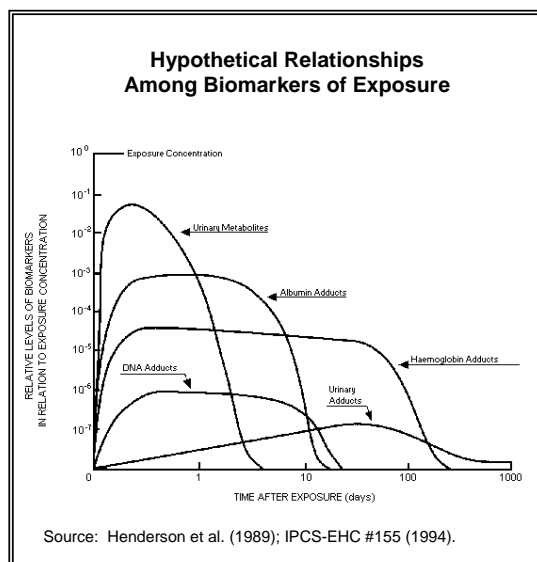
metals (http://www.epa.gov/ttn/fera/trim_gen.html); EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model, a probabilistic, physiologically based model that simulates aggregate human exposures and doses for various population cohorts of interest (Dang et al., 2003; Zartarian et al., 2000); EPA's Dietary Exposure Potential Model (DEPM) (Tomerline et al., 1997); RESRAD, a generic exposure model developed by the U.S. Department of Energy for risk assessment of radionuclides (U.S. DOE, 2001; LePoire et al., 2000); and 3MRA, a multimedia, multi-pathway, multi-receptor exposure model developed for screening-level risk-based assessment of chronic exposures to chemicals released from land-based hazardous waste management units (<http://www.epa.gov/ceampubl/mmedia/3mra/>).

4.2.7. Biomarkers

Risk assessors may find biomarkers of exposure, effect, and susceptibility useful as basic tools (IPCS, 2001, 1994). Centers for Disease Control (CDC) and the National Health and Nutrition Examination Survey (NHANES) are currently developing a national database to quantify and characterize body burdens (based on human blood and urine surveys) that includes Pb, Hg, Co, uranium (U), antimony (Sb), barium (Ba), Be, Cs Mo platinum (Pt), thallium (Tl), and tungsten (W) (CDC, 2005). Risk assessors can use this survey as a

baseline measure against which the levels in receptor population individuals can be compared. The data are summarized in age, gender, and ethnicity categories. NAS also has completed a substantial amount of work in this area (NAS/NRC, 2006).

Integration of exposures across media, route, and time of exposure can be reflected in biomarkers of exposure. A biomarker of exposure is a measure of cumulative exposure to a metal and also of metal actually existing in the body, as occurs with chronic exposure to metals. However, such an approach may not be appropriate for metals that are not extensively bioaccumulated in tissues, and it does not differentiate between metal present in a tissue in a sequestered or inactive form and metal engaged in toxic or pathological processes. The approach also does not differentiate naturally occurring exposures from those due to added metals. For example, arsenobetaine is a nontoxic organic form of As found naturally in shrimp and other seafood. The analysis of total, unspicated urinary As, without recognition of an individual's dietary history, could lead to an overestimation of exposure if the risk assessor does not account for seafood consumption (NAS/NRC, 1999). Thus, use of biomarkers increases the need for comprehensive, multipathway assessments of exposure. When available, reference or baseline levels of biomarkers of exposure should be incorporated into the assessment.



4.3. HAZARD CHARACTERIZATION

Hazard identification (or hazard characterization) is “the determination of whether exposure to an agent can cause an increased incidence of an adverse health effect, such as cancer or birth defects, and characterization of the nature and strength of the evidence of causation” (NAS/NRC, 1994b). This includes identification of the target organ(s), consideration of any route-specific issues, evaluation of the adversity of the effects observed, and consideration of relevance to humans. Key points and metals-specific concepts to be considered in hazard characterization are detailed in the following sections.

4.3.1. Mixtures and Interactions

In most settings, individual metals exist as components of mixtures with other metals and/or organic substances (ATSDR, 2004; NRC, 1988). Effects of the metals in mixtures may be synergistic, additive, subadditive, potentiating, and/or antagonistic. Interactions among metals occur by competition for binding locations on specific enzymes or on cellular receptors during the processes of absorption, excretion, or sequestration at the target site. The presence, amounts, and interactions of all inorganic metals are important when considering and evaluating the effects of exposure and resulting human health risk assessment.

Metals usually exist as components of mixtures with other metals and/or organic substances (ATSDR, 2004; NRC, 1988). Because the information or guidance on risks of metal mixtures is limited, risk assessors should follow published guidance for the human health risk assessment of chemical mixtures in general (U.S. EPA, 2000b, 1986) and cumulative risk guidance (U.S. EPA, 2003e).

Only a few controlled studies exist on the interactions of metals relevant to levels found in the environment (see ATSDR, 2004, on mixtures of (1)As, Cd, Cr, and Pb; and (2)Cu, Pb, Mn, and Zn). Risk assessors may use the current default approach, which assumes additivity of the doses for each metal as it will produce estimates that are overly-cautious. This approach, which involves calculation of a hazard index (HI), is most appropriate for chemicals that produce the same effects by similar modes of action (MOAs). However, differing potencies of metals with similar MOAs should be accounted for by converting chemical concentrations into an equitoxic dose using either toxic units (TUs) or toxicity equivalence factors (TEFs). In the case of chemicals with different MOAs, the risk assessor should consider estimating separate effect-specific HIs for each chemical in the mixture

Metal-Binding Proteins

Metallothioneins (Ag, Hg, Cu, Bi, Cd, Pb, Zn) **t**
Transferrin (Fe, Al, Mn) **t**
Ferritin (Fe, Cd, Zn, Al, Be) **s**
Ceruloplasmin (Cu, Fe) **tr**
Lead-binding protein(s) (Pb) **s**
Membrane carrier proteins **t**
s = storage; **t** = transport; **tr** = transform

using the RfD as the toxicity value for each effect. Newer EPA guidance provides a number of quantitative approaches for characterizing mixture risks (described in detail in U.S. EPA, 2000b, 1986).

The terms *molecular mimicry* and *ionic mimicry* have been applied to situations in which a metal forms a complex with an endogenous ligand and the resulting compound mimics the behavior of a normal substrate, disrupting normal function (Ballatori, 2002; Clarkson, 1993). Molecular or ionic mimicry may be viewed as a form of metal-metal interaction. Most examples involve the replacement of an essential metal with a nonessential metal. For example, Cd can mimic and substitute for Zn and Ca. Additionally, many different proteins in the body complex with metals which may modify their toxicity and kinetics (e.g., some metals bind with albumin for purposes of transport in the circulatory system and across cell membranes or within cells). Some proteins have different binding kinetics for the various metals, resulting in specific protein-metal interactions. Risk assessors should be familiar with these metal-binding proteins to correctly interpret the bioavailability of individual metals within a mixture and the potential use of protein expression as a biomarker of metal exposures.

Many of the interactions between essential metals are related to maintaining optimal nutritional levels by synergisms and antagonisms at both physiological and extrinsic (dietary) sites. World Health Organization (WHO) publications (IPCS, 2002; WHO, 1996) have summarized these homeostatic interactions, which are often complex (e.g., excess Ca in the diet may induce signs of Zn deficiency, even if the Zn intake is normal). Similarly, excess Zn in the diet may aggravate Fe deficiency.

Interactions between essential and nonessential metals are very common (e.g., Cd uptake can mimic that of Zn). Similarly, among anions, mimicry of the sulfate and phosphate ions occurs. However, the risk assessor should be aware that validated data in humans are rare, and that applications of this phenomenon are best limited to screening-level assessments. Two nonessential metals may compete for passive transport across common sites on a membrane or with an essential metal on an active binding site. These effects may not be additive and likely relate to relative binding strength. One metal may affect one site and another metal may affect a different site; this can include both active and passive transport or binding sites and may or may not include interactions with essential metals. These effects often will be additive. The risk assessor should be familiar with the MOAs of each metal of concern to develop at least a general understanding of whether the mixture effect is likely to be additive or more than additive.

Metals can be active at most cellular sites where organic toxicants have their effects and directly interfere with receptor activation (Stoica et al., 2000), ion channel regulation (Kiss and Osipenko, 1994), cell signaling (DeMoor and Koropatnick, 2000), cell adhesion (Prozialeck et al., 2002), and gene transcription (Meplan et al., 2000). Thus, metals are not readily distinguished from organic substances in the range of their potential mechanisms of action at the cellular and molecular level, so the risk assessor can transfer knowledge about toxicity across

chemicals. Additionally, co-occurrence of metals with organic substances can change the bioavailability and increase or decrease absorption. For example, in the diet, citrates and histidine are known to enhance Zn absorption, whereas ascorbate can modify Fe-Cu antagonisms. Low protein content may increase the absorption of Cd and Pb, and oral contraceptives may influence the metabolism of Fe, Cu, and Zn. The risk assessor should be aware of these conditions to avoid over- and underestimating risk.

4.3.2. Essentiality

Certain elements are nutritionally essential to humans and play a key role in physiological or biochemical processes (NAS/IOM, 2003; IPCS, 2002; WHO, 1996). Elements essential to other organisms may not be essential to humans and vice versa. Adverse nutritional effects can occur if essential metals are not available in sufficient amounts, and nutritional deficits also can be adverse and increase the

vulnerability of humans to other stressors, including those associated with other metals.

Essentiality should be viewed as part of the overall dose-response relationship, and *reference doses* designed to protect from toxicity of excess should not be set below doses identified as essential.

Metals that are currently deemed nutritionally essential for humans are Co, Cr III, Cu, Fe, Mg, Mn, Mo, Se and Zn (Table 4-1). Some metals (e.g., B, Ni, Si, V, and perhaps As), while not essential to human health, may have some beneficial effects at low levels of exposure (NAS/IOM, 2003). Risk assessors should consider the essential elements as comprising three groups: those that are cations (Zn, Fe, Cu, Mn, Cr), those that are anions (Mo, Se), and those that are a bio-inorganic complex (i.e., the Co complex, cobalamin). The homeostatic mechanisms differ for each group, and risk assessors can use this knowledge to generally classify the types of health effects that might occur and the potential bioavailability of the metal. In general, the gastrointestinal tract and the liver regulate the uptake and transfer of cations (e.g., Fe, Zn, Cu). The anionic group is more water-soluble and is less reactive with N, S, P, O, and hydroxide groups than are cations. They are absorbed very efficiently through the intestine and their subsequent compartmentalization and excretion is by manipulation of their oxidation and methylation states; total body burden is regulated by renal excretion. The risk assessor should be aware that homeostatic controls do not typically apply to effects at the portal of entry, so effects can be seen at lower doses than those required for systemic responses.

The risk assessor should view *essentiality* as part of the overall dose-response relationship. The risk assessor should use the entire dose-response relationship, from very low (inadequate) doses to high (toxic) doses (see text box) when determining an acceptable upper

Essentiality

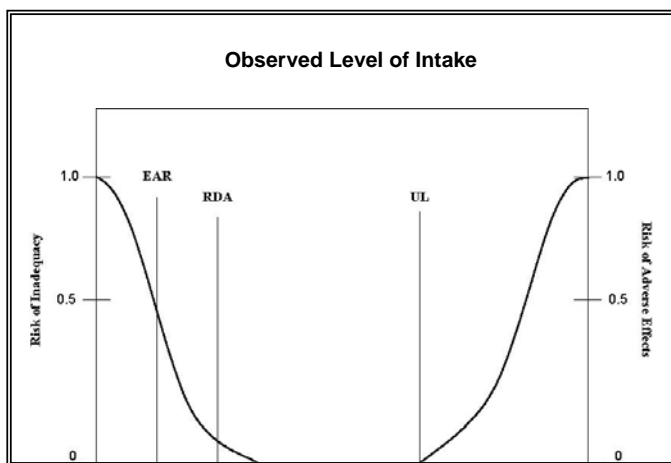
Essentiality should be viewed as part of the overall dose-response relationship. The shape of this relationship can vary among organisms. For a given subpopulation, reference doses designed to protect from toxicity of excess should not be set below doses identified as essential for that subpopulation.

Table 4-1. Metal essentiality for humans

Nutritionally essential metals	Nutritionally nonessential metals	
Cobalt II, III Chromium III Copper 0, I, II Iron II, III Magnesium II Manganese II, IV Molybdenum IV, VI Selenium II, IV, VI Zinc II	Aluminum III Antimony III, V Arsenic III, V Barium II Beryllium II Bismuth III, V Boron III Cadmium II Cesium* I Chromium VI Gallium* III Germanium* IV Gold 0, I, III Indium* III Lead II, IV Lithium I Mercury 0, I, II	Nickel II Niobium* V Palladium* 0, II Platinum* 0, II, IV Rubidium I Silicon* IV Silver 0, I, II Strontium II Tellurium* II, IV, VI Thallium I, III Tin II, IV Titanium IV Tungsten VI Uranium IV, VI Vanadium III, V Zirconium* IV

* Limited human data for these metals.

exposure limit. Several agencies have developed guidance for selecting a benchmark dose that is not too low (and, therefore, likely to result in deficiency) or too high (and likely to result in toxicity to some segment of the population). IPCS (2002) guidance describes the use of an “Acceptable Range of Oral Intake” (AROI), which estimates the minimal requirement to prevent deficiency and an



upper limit that will produce toxicity. The NAS Food and Nutrition Board (FNB) in conjunction with the Institute of Medicine (IOM, 2001; NAS/IOM, 2000) developed the Dietary Reference Intakes (DRIs) program and reformulated RDAs (now known as RDIs) using the estimated average requirement (EAR) or adequate intakes (AIs). They also developed a tolerable upper intake level (UL), which is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. The UL is based on a risk assessment model similar to that used by EPA to set the RfDs and is intended to protect the population from adverse health effects resulting from excess exposure to a compound. ULs are available for all the essential metals and for B, Ni, and V. ULs do not take into account sensitive

or immuno-compromised populations. ULs may differ from RfDs because they are derived from human studies rather than animal studies and use smaller uncertainty factors. Additionally, the risk assessor should be cautioned that RfDs are intended to cover sensitive subpopulations, whereas RDAs are estimated to satisfy the nutritional needs of 97.5% of the healthy U.S. population. RDAs are specific to different age groups and genders, with listings for 16 different age-sex and six age-pregnancy combinations (NAS/IOM, 2003).

4.3.3. Forms of Metals

Unlike organic chemicals, metals are neither created nor destroyed by biological or chemical processes. However, these processes can transform metals from one valence state to another and can convert them between inorganic and organic forms. Information developed for one form of a metal may not be directly applicable to other forms. Different valence states (species) of the same metal affect bioaccessibility and bioavailability, and they elicit different responses in the human body. The particle size and environmental matrix (water, soil, air), within which the metal is embedded, influence exposure amount, rate, and route, particularly for the inhalation pathway, which can then result in different target organs and response levels. Therefore, the risk assessor should consider which form of the metal of interest is being assessed. If exposure or effects information has been developed for a different metal species, the risk assessor should either make appropriate adjustments or acknowledge this as a significant uncertainty in the Risk Characterization. For example, Cr(III) is essential in the diet, whereas inhaled Cr(VI) is carcinogenic.

Risk assessors should be aware that information developed on the health effects of one form of a metal may not be directly applicable to other forms, particularly organometallics; other guidance documents should be consulted when conducting risk assessments for organometallics.

4.3.4. Toxicokinetics/Toxicodynamics

Homeostatic mechanisms such as binding of metals to proteins can introduce significant complexities to hazard assessments for metals, with significant quantitative effects once these mechanisms are overwhelmed. Certain metal compounds bioaccumulate in human tissues, and it is important to recognize that such bioaccumulation is related to toxicity (SAB, 2006; see Section 2.3.1 for a definition and more detailed discussion of bioaccumulation). Since not all tissues may be of “interest” from a human health perspective, net accumulation in human tissues may or may not be relevant in the hazard characterization of metals (see, for example, Section 4.3.4.2 for a

Toxicokinetics

Toxicokinetics describes the series of processes that dictate the disposition of a substance in or on the body after exposure occurs and processes related to deposition on the body surfaces (also considered in exposure assessments), absorption, distribution, metabolism, and excretion (ADME).

discussion of metal sequestration and subsequent remobilization). Further, there are no available simple metrics that allow quantification of the potential for human bioaccumulation of metals, although a full pharmacokinetic model can be used to estimate metals bioaccumulation and distribution in human tissues. Additional discussion of the potential for remobilization of sequestered metals is in section 4.3.4.2. All these processes can be described through the use of physiologically based pharmacokinetic (PBPK) models. Integrated descriptions provide metrics of internal dose (including biological markers of exposure) that can be used by risk assessors to improve the quantitative basis of dose-response assessments. Unique features of metals that result in differences in toxicokinetic behavior of metals as compared to organic substances are shown in Table 4-2.

Bioaccumulation of metals is the net accumulation of a metal in the tissue of interest or the whole organism that results from *all environmental exposure media*, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a net mass balance between uptake and elimination of the metal (SAB, 2006).

Table 4-2. Summary of major differences in kinetic behavior of organic compounds compared to metals and inorganic metal compounds in humans

Organics	Metals
<i>Tissue uptake</i> is most commonly a blood flow-limited process, with linear partitioning into tissues.	Metals and their complexes are often ionized, with <i>tissue uptake</i> (membrane transport) having greater potential to be diffusion-limited or to use specialized transport processes.
<i>Metabolism</i> is generally extensive and often species-specific.	<i>Metabolism</i> is usually limited to oxidation state transitions and alkylation/dealkylation reactions.
<i>Persistence</i> in body fat is common because of lipid solubility (not capacity-limited).	Often <i>sequestered</i> , bound to specific plasma or tissue proteins (intrinsically capacity-limited) or bone.
Due to complex metabolism, organics may be <i>eliminated</i> by excretion in urine after biotransformation from lipophilic forms to hydrophilic forms, in bile after conjugation to large organic molecules, or in exhaled air if not metabolized.	Predominantly <i>eliminated</i> in urine because metal compounds are generally small molecules and are hydrophilic. As a result of protein binding, may be excreted via hair and fingernails.
Generally substance-specific <i>homeostatic mechanisms</i> are not available.	Essential metals have <i>homeostatic mechanisms</i> that maintain optimum tissue levels over a range of exposures.
<i>Interactions</i> with other structurally similar compounds may occur, especially during metabolism.	<i>Interactions</i> among metals and between metals and organics are numerous and occur commonly during the processes of absorption, excretion, and sequestration.

Source: Adapted from Golub et al. (2004).

4.3.4.1. Absorption

Absorption is a process by which an administered substance enters the body. *Bioavailability* is a term often used to describe the degree of absorption. Two elements of the absorption process are critical for evaluating systemic doses of metal compounds, both the degree and rate of absorption. Although information on both of these parameters is ideal for developing a quantitative estimation of systemic doses, information on the degree of absorption is more commonly available for most chemicals. Metals have a number of unique properties that impact their absorption across biological membranes. Key factors affecting the absorption of metals include solubility, particle size, valence state, lipophilicity, and the exposure matrix. Soluble forms of the metal are more readily absorbed since the metal ion itself is typically the absorbed entity. The bioavailability of metals increases as particle size decreases. However, in the lung particle size also determines the site of deposition and thus the clearance mechanisms that can ultimately result in systemic uptake (via transport to the lymph system following macrophage engulfment) or the GI tract (via mucociliary transport). Chemical speciation in terms of valence state can affect absorption. Recent progress in identifying metal transporters suggests that generalizations are not appropriate, and each metal should be assessed in terms of its ability to access transporters and the presence of transporters in potential target organs. In general, lipophilic compounds will be absorbed more readily than hydrophilic ones. For example, human skin is not very permeable, and it provides a good barrier against dermal absorption of metals and metal compounds; elemental Hg and dimethyl Hg are notable exceptions. Risk assessors should note the complexities in absorption processes since they have direct implications on metals risk assessment, primarily in requiring detailed consideration in extrapolating across different exposure conditions or animal species. Absorption can vary dramatically for different forms of the same metal, for the same form of metal in different matrices, among different species, and across different routes of exposure. Therefore, it is not appropriate to assume concordance in absorption of metal compounds without a detailed evaluation (and documentation) of the scientific basis for such an assumption. For example, empirical information on dermal absorption of metals should be consulted when available (Stauber et al., 1994; Wester et al., 1992; Hursh et al., 1989; Ilyin et al., 1975), and similar considerations apply to other routes of exposure.

4.3.4.2. Distribution

The unique features of metals influence their distribution to potential target organs and the subsequent target tissue doses. The distribution of metals reflects their transport and accumulation in the body within tissues, blood or plasma, or other extracellular space. Partitioning to blood and cellular components, particularly via interactions with proteins, is of particular importance for metal risk assessment. Retention in tissues of metals or metal

compounds generally is related to formation of inorganic complexes or metal protein complexes (e.g., Pb in the bone compartment and Cd in tissues bound to low-molecular-weight metallothionein proteins). Risk assessors should be aware that retention of metals in the body by protein binding or sequestration in a nontoxic form allows the metal to reside in the body without producing a toxic or pathological effect. For example, As and Hg have relatively short biological half-lives that can be measured in days, whereas Cd and Pb can be bound or sequestered in inactive forms for years. Cd is retained in soft tissues (e.g., liver and kidney) for 10 to 20 years by intracellular binding with metallothionein. Metal binding to proteins is capacity-limited, and toxicity to target organs occurs when the binding capacity is exceeded. Thus, the potential for toxicity exists in older adults for metals with long half lives that are initially adequately sequestered. Conversely, retention in tissues is a dynamic equilibrium and can be a source of internal exposure long after the external exposure source has been removed. For example, Pb in bone can be mobilized during pregnancy and lactation or as a result of osteoporosis (USEPA IRIS, <http://www.epa.gov/iris/subst/0277.htm>). The risk assessor should consider all the aspects of metal distribution in the body (i.e., binding and sequestration plus release processes) when estimating likely target dose. The risk assessor should also note the uncertainty associated with lack of information to complete a quantitative analysis of these processes during the Risk Characterization.

4.3.4.3. *Metabolism*

Metabolism of metals is limited to oxidation-reduction reactions or alkylation/dealkylation reactions. In these reactions, new inorganic species or metal organic complexes may be formed, but the metal ion persists. Nevertheless, differences in these transformation pathways among human populations or across species have practical implications for risk assessment because different species of the same metals often have very different toxicities. Because of this, the risk assessor should fully explore available data on metal metabolism. For example, As can be metabolized to organic forms that are less toxic than the inorganic As to which an individual is initially exposed.

4.3.4.4. *Excretion*

Risk assessors should be aware of the number of qualitative differences in metal excretion as compared to organic compounds. These include the greater likelihood for excretion in urine and the propensity for metals to be excreted via hair and nails. In addition to reducing the target dose, risk assessors can use these excretion routes to develop biological markers of exposure for many metals.

Although metals share many similar characteristics, their excretion kinetics can vary dramatically, primarily because of differences regarding sequestration in bone or binding to

specific proteins. This reduces the rate of excretion (or generates a biphasic excretion curve with two or more distinct excretion half-lives). Risk assessors should assess each metal individually to incorporate excretion rates in the calculations of target dose and subsequent hazard assessment.

4.3.4.5. *Kinetic Modeling*

Physiologically based pharmacokinetic/pharmacodynamic (PBPK/PBPD) modeling of metals entails the mathematical description and modeling of their absorption, distribution, metabolism, and excretion (ADME). A typical PBPK model consists of multiple compartments representing tissues or tissue groups that are linked by blood flow. PBPD models describe the relationship between target tissue dose and health endpoints or target tissue effects. Combined use of PBPK and PBPD models provides understanding of the complex relationships between exposure and target organ effects. Risk assessors may find that these models are valuable risk assessment tools for purposes of interspecies, high-dose/low-dose, route-to-route, and exposure scenario extrapolations (Krishnan and Andersen, 1994). A PBPK model allows the risk assessor to define the relationship between external exposure and an internal measure of a biologically effective or toxic dose in both experimental animals and humans, thus increasing the precision of extrapolating effects thresholds to humans. Use of PBPK models can account for nonlinear uptake, metabolism, and clearance; toxicity associated with products of metabolism rather than the parent chemical only; and tissue interactions. The underlying assumption of PBPK is tissue dose equivalence, i.e., that health effects are caused by the toxic form(s) of the chemical measured at the biological target (Krishnan and Andersen, 1994).

PBPK models historically have been developed and used for risk assessment mainly with volatile organic compounds (VOCs) (e.g., methylene chloride) (Andersen et al., 1987), but PBPK models have recently been applied to some metals (White et al., 1998; Clarke, 1995). There are currently three main Pb risk assessment PBPK models. *The O'Flaherty model* (O'Flaherty, 1995) is a PBPK model for children and adults. It includes the movement of Pb from exposure media (i.e., intake via ingestion or inhalation) to the lungs and gastrointestinal tract and subsequent exchanges between blood plasma, liver, kidneys, and richly and poorly perfused tissues; and excretion from liver and/or kidney. *The Leggett model* (Leggett, 1993) allows risk assessors to simulate lifetime exposures and can be used to predict blood Pb concentrations in both children and adults. The EPA has performed a comparison of these adult Pb risk assessment models

<http://www.epa.gov/superfund/lead/products/adultrevie>

Metal Toxicity

The organ or tissue in which metal toxicity occurs may differ from the organ or tissue(s) in which the metal accumulates and may be affected by the metal's kinetics. Effects at the portal of entry do not depend on bioavailability. Both the exposure route and the form of the metal can affect a metal's carcinogenic potential and its noncancer effects.

[w.pdf](#)) . EPA developed the Integrated Exposure Uptake Biokinetic (IEUBK) model to predict Pb levels in children (U.S. EPA, 1994a) and recommends that it be used as the primary tool for Pb risk assessment at Superfund and RCRA corrective action sites (OSWER Directive, 1998; <http://www.epa.gov/superfund/lead/products/oswer98.pdf>).

Risk assessors can review differences in kinetic behavior between metals and VOCs in O’Flaherty (1998). In brief, these include: (1) oral bioavailability, (2) inhalation bioavailability, (3) cellular uptake, (4) nutritionally essential and nonessential metal interactions, (5) protein-binding behavior and function, (6) incorporation into bone or hair, (7) metabolism, and (8) excretion. Moreover, risk assessors should keep in mind that many of the processes controlling the disposition of metals are intrinsically capacity-limited and can result in extended residence times. Risk assessors should use multiple lines of evidence to understand the kinetics and, therefore, the hazard of metal sequestration and elimination. The major challenge faced by the risk assessor when using PBTK models for metals is to balance the complexity of the biology with the data available to parameterize the model. Estimation of many parameters from the same data or insufficient data (over-parameterization) leads to greater uncertainty in model predictions and limits the utility of the model for regulatory purposes.

4.3.5. Metal Toxicity

Diversity in observed toxicities of different metals likely reflects the variety of biochemical mechanisms by which they exert their effects and variability in their toxicokinetic properties. At least five metals are known carcinogens, and several other effects of metals are also well documented, including effects on the neurological, cardiovascular, hematological, gastrointestinal, musculoskeletal, immunological, and epidermal systems.

4.3.5.1. *Noncancer Effects of Metals*

Metals and metal compounds have very diverse toxicological profiles. For risk assessment purposes, selected critical effects serve as the basis for deriving threshold or benchmark toxicity values (e.g., RfDs) and are defined as “the first adverse effect, or its known precursor that occurs to the most sensitive species as the dose rate of an agent increases” (U.S. EPA, 2005). Both the mechanism of toxicity and the critical effect may vary with the form of the metal. Additionally, short-term exposures may produce target organ effects very different from those produced by a similar dose over a longer period of time. Short-term, high-level exposure by ingestion may give rise to well-recognized acute toxicity syndromes, usually involving the gastrointestinal tract initially and possibly, secondarily involving the renal, cardiovascular, nervous, or hematopoietic systems. Survivors of acute high-dose As ingestion usually experience multiple organ effects, sometimes with long-term sequelae. Long-term, low-dose exposures from ingestion of metals in food and water generally cause an accumulation in

target organs over time. Such exposures can involve any organ system but do not usually produce overt gastrointestinal symptoms. For example, low-level, long-term exposure to Cd in food—sometimes combined with inhalation exposure from cigarette smoking—will cause Cd to accumulate in target organs (e.g., kidney) but will not produce any obvious clinical effects until “excess” capacity is diminished to a point where the normal function is lost (e.g., onset of renal disease and/or osteoporosis later in life).

In addition to considering systemic effects, the risk assessor should also examine portal-of-entry effects. Unlike systemic effects, which may be route-independent, portal-of-entry effects are not observed following other routes of exposure. For example, dermal irritation, sensitization, and allergic responses from metals can occur without absorption and systemic responses.

4.3.5.2. Carcinogenic Effects of Metals

At least five transition metals—As, Cd, Cr(VI), Be, and Ni—are accepted as human carcinogens in one form or another or in particular routes of exposure (IARC, 2004b; NTP, 2002) and inorganic Pb compounds are considered probable human carcinogens by EPA’s IRIS program, while IARC (2004a) has concluded that there is limited evidence of carcinogenicity to humans (see: <http://www.epa.gov/iris/subst/0277.htm#carc> and <http://monographs.iarc.fr/htdocs/announcements/vol87.htm>). Other metals have mixed evidence regarding potential carcinogenicity. Therefore, risk assessors should pay careful attention to approaches for cancer risk assessment as applied to metals. Several guidance documents are available for use by the risk assessor in developing or interpreting cancer risk assessments (e.g., U.S. EPA, 2005), as are international efforts that provide guidance on assessing human relevance of tumors identified in animals (Cohen et al., 2004).

Nickel and Pb compounds and Cr and Cr compounds are well-established contact allergens. Other metals that have been cited as contact allergens include Cu (WHO/IPCS, 1998), Co salts (AIHA, 2003), organomercurials (AIHA, 2003), Be (IPCS, 1990b), palladium (Pd) (Kimber and Basketter, 1996), and gold (Au) (Kimber and Basketter, 1996). Although there is some connection between skin and respiratory sensitization, it does not follow exact rules, and the dermal mode is a much more common reaction to metals.

A key consideration for the risk assessor in cancer risk assessment is the determination of the MOA of carcinogenesis, a general description of how the chemical causes cancer. The MOA determines human relevance of observed animal tumors, any route-specific differences (e.g., carcinogenic at the portal of entry via the inhalation route, but not carcinogenic via the oral route), and the approach used for extrapolation from experimental doses in animals to environmentally relevant human doses. In particular, the MOA evaluation is a key consideration in whether a linear or nonlinear approach is used to extrapolate to low doses. The MOA is

known for some, but not all, metals. For those for which the MOA is unknown, the risk assessor should refer to the Cancer Guidelines (U.S. EPA, 2005) for guidance.

4.3.5.3. *Issues Related to Evaluation of Toxicity Tests for Metals*

As with any hazard assessment, risk assessors prefer a robust dataset on toxic responses of the metal(s) of concern for key endpoints (e.g., irritation and sensitization, systemic noncancer toxicity, and genotoxicity or tumorigenicity). In many cases, metals will be well-studied, and thus, human studies (epidemiology, controlled clinical studies, or case reports) will be available to aid in hazard characterization. For metal compounds for which adequate human data are not available, the risk assessor must rely on animal toxicity studies. U.S. EPA has established guidelines for assessing the adequacy of a database for derivation of chronic human health risk values such as RfDs and RfCs (U.S. EPA, 2002a) and has provided guidance for evaluating the “weight of evidence” for carcinogenicity (U.S. EPA, 2005). These generic guidelines are applicable to metals as well as organic compounds as long as the risk assessor considers the following metal-unique aspects of hazard determination:

- **Adequate controls.** When a salt of a metal is administered to the test animals, the risk assessor should evaluate that a suitable control group was used, specifically that any potential for salt-induced toxic responses is appropriately assigned probable cause.
- **Dosing solubility, ionization, hydration, and speciation of metals administered in water.** Metal compounds may be in suspension or in solution and may be differentially hydrated depending on the concentration in which they are prepared and the length of time the preparation stands, potentially resulting in different pharmacokinetic and toxic properties. Water pH and mineral content also are relevant factors to be considered by the risk assessor.
- **Trace element content of food and drinking water.** Because of the well-known interaction of metals with essential trace elements, the trace element content of animal feed and drinking water or of vehicles used for gavage or injection studies should be reported or controlled. Inconsistent results across experiments could be due to this factor.
- **Acute stress in the experiment.** A component of acute stress in the experiment can induce hepatic metal-binding proteins (acute phase proteins) and alter the toxicity of a given administered dose.

To achieve an adequate internal dose for the study of toxicity, animal toxicologists often use bioavailable forms 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, Al researchers commonly use aluminum lactate, which is known to reliably provide elevated tissue concentrations in laboratory animals, or aluminum maltolate, which

provides a stable ion pool in water solution. However, a risk assessor is very unlikely to conduct an assessment of Al in its lactate or maltolate form. Thus, the risk assessor should be aware that failure to adjust the toxicity data generated from water-soluble metal species to the appropriate, less soluble species of concern introduces uncertainty. There are both direct and indirect approaches to address the relative bioavailability of metals in the environment: (1) conduct new animal toxicology studies using the metal form encountered in the site assessment; (2) use adjunct scientific data to derive an adjustment to the effective dose identified in the animal study (e.g., data on the distribution of chemical forms of the metal in the environment or at a contaminated site); or (3) use a default assumption that the metal in the environmental samples is the same as that tested. The first approach is more scientifically sound but often is precluded by time and financial resource limitations; the third option generally is the most health-conservative.

A fourth alternative to conducting site-specific assessments is for the risk assessor to estimate bioavailability through solubility studies or limited bioavailability studies of specific samples from the site. For example, arsenic bioavailability has been estimated for soils from various contaminated sites (Ng et al., 1998; Freeman et al., 1995, 1993) 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).

4.3.6. Dose-Response Assessment

The result of the hazard characterization is a determination of the key noncancer and cancer endpoints related to exposure to the metal of interest. The risk assessor then uses these data as the input to the dose-response assessment to “characterize the relationship between exposure or dose and the incidence and severity of the adverse health effect” (NAS/NRC, 1994b). Assessors should consider the factors that influence dose-response relationships, such as intensity and pattern of exposure, age, and lifestyle variables. Traditionally, separate approaches have been used for dose-response assessment for noncancer and cancer endpoints. For noncancer endpoints, the result of the dose-response assessment is an RfD for oral or dermal exposure or an RfC for inhalation exposure. For cancer assessment, the approach depends on the chemical’s MOA. Classically, the result of the cancer assessment is a measurement of the risk per unit dose, either as a slope factor or unit risk.

A key consideration for the risk assessor when deriving metal dose responses is to express the exposure potential and the toxic response as the same metal species. In general, for systemic effects of soluble metal salts, the risk assessor should express toxicity in terms of the dose of the metal ion rather than the metal salt. In contrast, if the toxicity is related to a specific compound, particularly for portal-of-entry effects, risk assessors should express it in terms of the compound, rather than the ion. These differences should be considered when applying toxicity values in risk assessments. For example, in IRIS, Se is listed as “selenium and compounds,” and there are separate assessments for “nickel, soluble salts,” “nickel subsulfide,” “nickel refinery

dust” (a mixture), and “nickel carbonyl” (a highly reactive compound that behaves differently from other nickel compounds). In some situations, the toxicity of the anion needs to be considered. For example, there are separate IRIS documents for Ag and silver cyanide. However, careful consideration of the chemical form has not been applied historically to all such documents, and the risk assessor should carefully consider the applicability of the chosen toxicity values to the chemical forms of interest, paying close attention to solubility, bioavailability, and physical/chemical properties as well as available toxicity data.

A related issue is whether the toxic response is reported in terms of the added metal in the diet or the total metal (i.e., whether the amount of trace elements in the control diet in the animal studies is included in the dose calculations). Risk assessors should carefully review the supporting documentation for toxicity values to determine precisely what is being reported and to account for any potential interactions among dietary metals. The assessor also should consider whether the study provided adequate levels of trace elements so that the observed toxicity is not secondary to some unrelated deficiency.

Dose-response assessments for some metals are based on data from human occupational studies. While derivation of the dose-response value (e.g., the RfC, RfD, or cancer slope factor) will have included some steps to extrapolate the occupational study data to environmental exposures (e.g., dosimetric and duration adjustments), the form of the chemical may merit consideration. For example, the occupational exposure will have involved a particular range of particle sizes, which may influence the response observed (U.S. EPA, 2002a).

Risk assessors should review RfDs derived for essential elements to ensure that they are not below required daily intakes. The RfD should not be below the general population RDA. This means that the risk assessor should give careful consideration to the appropriate size of uncertainty factors, which is often made easier by the frequent (although not uniform) availability of human data for relatively large and diverse populations. The only exception to the comparison between the RfD and nutritional requirements is that certain populations (e.g., pregnant women) may have higher nutritional requirements, while these levels could theoretically be toxic to other populations. In such cases, the risk assessor should be careful to avoid logical inconsistencies and to identify the sensitive population on which the RfD is based.

Considerations in Risk Characterization

Variability. Inter-individual biological differences exist within an animal or human population, or measurement differences exist owing to method imprecision.

Uncertainty. Data are unavailable.

Incertitude. Knowledge about key relationships is not available.

4.4. RISK CHARACTERIZATION

Risk Characterization is the final phase of the risk assessment process. It is the phase in which information from hazard characterization, dose-response assessment, and exposure assessment is considered together to determine the actual likelihood of risk to exposed

populations (NAS/NRC, 1994b). For example, inorganic As occurs naturally in food and water; thus, a risk characterization would integrate the currently accepted dose-response information for inorganic As with the exposure assessment information for a particular food or drinking water source, or for the national distribution of intake from food and water, to determine whether a potential problem exists. During Risk Characterization the uncertainties in the dose-response assessment, the uncertainties in the estimate of exposure derived for the scenario under evaluation, and the level of confidence in the overall determination of risk should be laid out. At the same time, Risk Characterization is the first phase in the risk management process, in which information from the characterization is integrated into the consequences of rule-making or risk management, such as consideration of cost, alternative solutions, political considerations, and community interactions.

<p style="text-align: center;">Risk Characterization</p> <p>Have the qualitative assessment, quantitative assessment, and key uncertainties regarding metals been presented in accordance with EPA guidelines?</p> <p>Do conclusions fully reflect risks in relation to ambient concentrations, essentiality of metals, chemical speciation, and information on human variability in sensitivity?</p> <p>Have assumptions and uncertainties been documented adequately?</p> <p>Have available data on mechanisms of action and metal interactions been fully explored in developing the quantitative assessment?</p>

Risk assessors should refer to guidance on Risk Characterization (U.S. EPA, 2000c) that identifies key goals and steps for a Risk Characterization. Each Risk Characterization should include three components: a qualitative summary of each section of the risk assessment, a numerical risk estimate, and a description of uncertainties. Since metal exposures often occur in the context of mixtures (either mixtures of metals of the same form, mixtures of different metal elements, or mixtures with organics), risk assessors should consult additional Risk Characterization tools developed for mixtures (U.S. EPA, 2000b, 1986). These guidelines specify that the characterization of risks from mixtures of metals (and other compounds) be based primarily on information about the types of interactions that might be present.

Risk assessors should include a discussion in the Risk Characterization of the sources of variability and uncertainty in the risk assessment process. This is particularly important for metals risk assessments given all the components above. These are in addition to the variability and uncertainties that are inherent in all risk assessments (e.g., animal-to-human toxicity extrapolations). Because information, knowledge, and tools are lacking for many of the metal-specific uncertainties, risk assessors should be particularly diligent in documenting whether these may result in an over- or underestimation of risk (i.e., result in a conservative risk estimate or not). It is likely that site-specific risk assessments will have fewer uncertainties than regional- or national-scale assessments because risk assessors have access to local data on key issues such as specific metal species, relative bioavailability, or current metal levels. For national or regional assessments, selection of ranges or specific numbers for these values will depend on the degree

of conservatism desired by the risk assessor and, therefore, should be clearly documented during the Risk Characterization phase.

5. AQUATIC ECOLOGICAL RISK ASSESSMENT FOR METALS

This chapter describes how to incorporate the metals risk assessment principles described in Chapters 1 and 2 into ecological risk assessments involving aquatic-based receptors. Specifically, the following discussion focuses on the relationship between each metal principle and components of the EPA's Framework for Ecological Risk Assessment (U.S. EPA, 1992a) and subsequent guidelines (U.S. EPA, 1998a). These components include Problem Formulation, Characterization of Exposure, Characterization of Effects, and Risk Characterization. The Problem Formulation phase consists of defining assessment endpoints, risk hypotheses, and a conceptual model to produce an analysis plan for the risk assessment. Chapter 2 discussed the consideration of the metals principles in the Problem Formulation phase. In this chapter consideration of the metals principles in the characterization of exposure, effects, and risk to aquatic organisms is discussed.

Consistent with the previously stated scope and purpose of this Framework, not all aspects of the ecological risk assessment process are discussed. Only those aspects of the aquatic ecological risk assessment process and associated technical issues with the greatest relevancy to the metals principles are included. Also emphasized is how the geographic scale (e.g., site specific, regional, national) and analytical scope (e.g., screening vs. definitive analysis) of aquatic risk assessments affect the extent to which the metals principles can be incorporated. Although these principles apply equally to risk assessments involving terrestrial-based ecological receptors, many of the methods and tools that can be used to implement these principles differ between the aquatic and terrestrial environments. Thus, a separate discussion of how the metals principles apply to ecological risk assessment in the terrestrial environment is provided in Chapter 6.

5.1. METALS PRINCIPLES

Metals have specific environmental and biotic attributes that should be considered in all risk assessments. Specifically, these attributes fall into the risk assessment paradigm as follows:

Background levels	Exposure Assessment
Mixtures	Exposure and Effects Assessment
Essentiality	Effects Assessment
Forms of metals	Exposure and Effects Assessment
Toxicokinetics/toxicodynamics	Exposure Assessment (bioavailability) and Effects Assessment (absorption, distribution, metabolism, and excretion [ADME] and toxicity)

5.2. CHARACTERIZATION OF EXPOSURE

The Exposure Characterization phase describes the potential or actual contact or co-occurrence of stressors with receptors. It includes analysis of stressor sources, their distribution in the environment, and the extent and pattern of contact or co-occurrence to produce an exposure profile for the ecological receptor(s) of concern. Further guidance on characterizing exposure in ecological risk assessments is found in U.S. EPA (1998a, 1992a).

Exposure Profile

The exposure profile should describe the exposure pathways from stressor source to the receptor, the exposure intensity, its spatial and temporal distribution of co-occurrence, and the impact of variability and uncertainty on the exposure estimates.

5.2.1. Background Levels

Background levels refers to those concentrations of metals that derive from natural as well as anthropogenic sources that are not the focus of the risk assessment. In aquatic ecosystems, metal concentrations vary widely over space and time owing to differences in watershed geology, hydrology, anthropogenic and natural loads from “nontarget” sources, and other factors. Depending on the magnitude of the exposure associated with these factors, background metal concentrations can account for a significant portion of total metal exposure. Furthermore, certain essential metals can bioaccumulate to high levels in some aquatic organisms (e.g., Zn in barnacles, Cu in crayfish) due to species-specific physiological requirements, regardless of source. Even some nonessential metals can naturally bioaccumulate to significant levels as a result of mimicry of essential metals or sequestration and storage. Thus, the risk assessor needs knowledge of background concentrations in order to characterize exposure and to differentiate risk associated with metal sources already in the environment from risk associated with the metal sources of concern in the assessment.

Depending on the design and context for the assessment, the risk assessor needs to address several questions and issues pertaining to background concentrations of metals. Obtaining reliable estimates of background concentrations can be challenging, particularly at larger spatial scales. Risk assessors are cautioned against using background metals in soils as surrogates for sediments due to differences in the biogeochemical processes between these two environments. Metal concentrations in

Environmental Background in Exposure Assessment

What are the environmental background concentrations at the site(s) of interest? How do they vary over relevant spatial and temporal scales?

What is the relationship between environmental background and toxicologically relevant metal concentrations?

Can natural and anthropogenic metal be distinguished?

To what extent are background concentrations being extrapolated over space and time?

What level of confidence (uncertainty) exists in the estimate of environmental background concentrations?

sediments can be impacted by sediment physicochemical composition and localized sediment transport processes. Fractionation of sediment cores, in combination with careful estimates of sedimentation rates, has been used to distinguish pre- vs. post-industrialized contributions of metals via atmospheric transport (e.g., mercury) (U.S. EPA, 1997b). Risk assessors may find this type of sediment core analysis useful for differentiating natural levels versus levels associated with anthropogenic sources.

Concentrations of metals in the water column vary over time and are highly responsive to hydrological changes. In site-specific risk assessments, the risk assessor may quantify background levels by measuring metal concentrations at sites upstream from the area of concern. National databases of metal concentrations in various aquatic media (sediments, water, biota) include the following:

- The EPA STORage and RETrieval (STORET) database (accessible at <http://www.epa.gov/storet/>);
- The National Sediment Quality Survey (NSQS) (accessible at <http://www.epa.gov/waterscience/cs/nsidbase.html>);
- Environmental Monitoring and Assessment Program (EMAP) (accessible at <http://www.epa.gov/emap/>);
- The National Stream Quality Accounting Network (NASQAN) (accessible at <http://water.usgs.gov/nasqan/>), and
- The Hydraulic Benchmark Network (HBN) (accessible at <http://ny.cf.er.usgs.gov/hbn/>).

The risk assessor should keep in mind that with the exception of the HBN, these databases have not been established to distinguish background concentrations from local, anthropogenic sources of metal loadings (e.g., industrial discharges, stormwater runoff) and, thus, may reflect significant anthropogenic loadings of metals to environmental media. The HBN was established to provide long-term measurements of streamflow and water quality in areas that are minimally affected by human activities. While the HBN contains long-term measurements of a number of parameters that are known to affect the bioavailability of metals (e.g., dissolved organic carbon [DOC], inorganic ions such as Ca and Mg, pH, conductivity), it does not contain information on metals of typical regulatory concern, with the exception of Al.

5.2.2. Forms of Metals

The physical and chemical forms of metals affect exposure, bioavailability, and subsequent effects and are influenced by physicochemical environmental conditions. National-level assessments involve a broad range of environmental conditions; therefore, the risk assessor

should account for different metal species in different locations and water body types. As assessments transition from national, to regional, and to local, the assessor should incorporate site-specific sediment and water quality parameters that influence metal speciation, complexation, and sorption onto biological surfaces (e.g., pH, organic carbon, inorganic ligands, Ca, Mg, sulfide). Speciation models (e.g., MINEQL) combined with biotic ligand models offer a framework for addressing the differential occurrence and toxicity of various metal forms. Risk assessors should be aware of the difficulty in applying this approach to assessments involving large regional or national scales because of the variability in model parameter values (including covariance among parameters) that occurs across locations. Information about the range of the input parameters can be derived from available databases (see Section 5.2.1), and the risk assessor can decide what value to use (e.g., minimum, maximum, mean) depending on the degree of conservatism desired in the assessment. The risk assessor should include this information in the Risk Characterization as part of the overall discussion of assumptions and uncertainties in the assessment. Risk assessors can directly assess the metal forms for site-specific assessments or estimate what these would be based on sediment/water parameters (see Section 3.1.3, Environmental Chemistry).

5.2.3. Exposure Pathway Analysis

For aquatic organisms, potential routes of exposure to metals include absorption across (or in some cases adsorption to) respiratory organs, dermal absorption, sediment ingestion, and food ingestion. Quantifying exposure and uptake by the respiratory route is a particular challenge to aquatic risk assessors because of the differing types of respiratory organs among aquatic species, the dynamic nature of the respiratory process in water, and the intimate contact between the receptor and metals dissolved in waters. Further

Exposure Routes

For aquatic organisms, pathways of exposure to metals include movement from water to sediments (and vice versa to a lesser extent) and through the food web; air deposition directly into aquatic systems or through run-off; and sedimentation from soils.

complicating the issue, some respiratory organs can also be involved in locomotion, excretion, ion regulation and the capture, sorting, and ingestion of food. Similarly, risk assessors may find the ingestion route 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 use of stable isotope techniques has contributed greatly to evaluating the role of diet in contaminant accumulation (including metals) by precisely defining trophic interactions (e.g., Kidd et al., 1995; Jarman et al., 1996). The absorption route can involve uptake across a phytoplankton cell membrane, amphibian skin, arthropod exoskeleton, the egg membrane, or the integument of an infaunal clam or annelid.

Despite the complexities associated with quantifying exposure of aquatic animals to metals from multiple routes of uptake, risk assessors can find a significant amount of information

on the relative importance of the different uptake pathways (Wang, 2002; Hook and Fisher, 2001b; Fisher et al., 1996; Bjerregaard et al., 1985). Applications of one-compartment biokinetic models using laboratory-based measurements of key model parameters (assimilation efficiency, metal uptake rates from water and food elimination rates) have been extended to field situations for populations of a diverse array of aquatic species, including freshwater and marine bivalves, various crustaceans such as copepods, amphipods, and crab, aquatic insects, and fish (e.g., Luoma and Rainbow, 2005; Stewart and Fisher, 2003; Griscom et al., 2002; Baines et al., 2002; Fisher et al., 2000, 1996; Roditi et al., 2000; Wang et al., 1996; Luoma et al., 1992). Site-specific model predictions for metal concentrations in animal tissues are strikingly close to independent field measurements for diverse water bodies, suggesting that it is possible for risk assessors to account for the major processes governing contaminant concentrations in aquatic animals and that laboratory-derived kinetic parameters are applicable to natural conditions (Luoma and Rainbow, 2005). Thus, these models provide tools for risk assessors to use when addressing metal exposure and uptake, and they can be used to determine the relative importance of different routes of exposure (Landrum et al., 1992; Wang et al., 1996).

Risk assessors should always consider temporal aspects of exposure, particularly in aquatic systems that respond to frequent shifts in hydrology. 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 rapid changes in pH/Eh associated with photosynthesis and respiration, hypolimnetic discharge from stratified reservoirs, biocide (e.g., copper sulfate) spraying, ingestion of prey items with seasonally high metal concentrations, surface waters receiving wastewater treatment plant effluent, urban storm water, snowmelt, and acid precipitation runoff. Transient metal concentrations may be orders of magnitude higher than typical or average concentrations but last for only a few hours. These episodic exposure scenarios have been poorly characterized for metals (Butcher et al., 2006). Any risk assessment for metals should clearly state all assumptions about duration of exposure and what uncertainties are added to the risk model as a consequence.

5.2.4. Fate and Transport of Metals

Risk assessors routinely use transport and fate computational models to describe and quantify exposure pathways. Models also are useful in situations where risk assessors need an estimate of future exposure levels that are expected to result from the implementation of some permitting action or remediation measures at local, regional, or national scales. Numerous models are available for use; most are based on the same fundamental principles. Metals are ubiquitous in the environment and within each media compartment they are present in association with air, water (freely dissolved metal or as organic and inorganic metal complexes), and particles (sorbed, precipitated, or incorporated within a mineral phase). The risk assessor can find a detailed discussion of the fate and transport of metals in Section 3.2. No single,

currently available model includes all the desirable metal-specific features for aquatic systems. Discussions of the family of available aquatic transport and fate models, as well as a number of chemical equilibrium models, may be found in Paquin et al. (2003).

5.2.5. Toxicokinetics and Toxicodynamics (Bioavailability and Bioaccumulation Issues)

5.2.5.1. Aqueous Phase

In the dissolved phase, metals can exist as free ions as well as in a variety of complexed forms. These forms, or species, are of key importance in understanding bioavailability, and the hazard and risk assessments of waterborne metals are complicated by the fact that metal species differ in their toxicological properties. For many metals in aquatic systems, it is the free ionic form that is most responsible for toxicity. For example, Cu^{2+} has been directly linked to toxicity in fish and invertebrates while Cu complexed by dissolved organic matter does not induce toxicity to the same degree (Ma et al., 1999; Erickson et al., 1996) because of its reduced availability for uptake by the organism. However, the risk assessor should be aware that although toxicity of metals bound to DOC is reduced, it is not eliminated entirely and can contribute to the total metal loading to an ecosystem and subsequent toxic effects (McGeer et al., 2002; Erickson et al., 1996). On the other hand, there are cases where nontoxic metal species are bioavailable and taken up by the organism but cause no adverse response (e.g., Ag-Cl complexes in rainbow trout) (McGeer and Wood, 1998). Risk assessors should recognize that the presence of metal within an organism cannot always be used as a surrogate for toxic response.

Risk assessors can choose among a variety of methods to account for relative bioavailability of metals in aquatic systems, including hardness adjustments, water-effect ratio (WER), Free Ion Activity Model (FIAM), and aquatic Biotic Ligand Models (BLMs) (Paquin et al., 2002a). Each method contains strengths and limitations and may not be amenable to all types of assessments (e.g., ranking/classification, national, and site-specific assessments). For example, adjustment of aqueous metal concentrations for differences in water hardness was among the first computational methods to account for bioavailability differences between the laboratory and the field when applying EPA water quality criteria. Although these adjustments are relatively easy to apply, they require empirical data to define the toxicity-water hardness relationship. Thus, they are more amenable to site-specific risk assessments, although even in those cases they do not account for other water quality factors that affect bioavailability (e.g., DOC, pH). The water hardness approach has been applied at the national level through a statement of water quality criteria as hardness-based equations rather than as single values. Risk assessors can choose to use ranges, means, or median values when conducting large-scale (e.g., regional) assessments, but they will need to acknowledge this uncertainty during the risk characterization phase.

Bioavailability adjustments using WERs incorporate the combined effects of all water quality parameters present in site water on bioavailability of metals of interest relative to what was measured in laboratory tests (U.S. EPA, 1994c). Thus, compared to hardness adjustments, WERs encompass a broader array of water quality factors that can impact bioavailability. However, WERs are relatively resource intensive (requiring toxicity testing), are applicable only on a site-specific basis, and are not easily adjusted to account for temporal or spatial variability.

This relationship between speciation and bioavailability also has been explained through the free ion activity model (FIAM, Campbell, 1995). This model produces speciation profiles of a metal in an aquatic system and provides insight into the relative bioavailabilities of the different forms of metal as well as the importance of complexation. Models available for the calculation of metal speciation in natural waters are reviewed in Section 3.1.5, Sediment Chemistry, and include MINEQL (Schecher and McAvoy, 1994; Westall et al., 1976), MINTEQA2 (Brown and Allison, 1987), CHESS (Santore and Driscoll, 1995), WHAM (Tipping, 1994), and PHREEQ (Parkhurst et al., 1980). The risk assessor should review Paquin et al. (2003) for a more in-depth understanding of these models and how to select among them for particular places and types of assessments.

The BLM approach successfully combines the influences of speciation (e.g., free metal ion, DOC complexation) and cationic competition (e.g., K^+ , Na^+ , Ca^{+2} , Mg^{+2}) on metal toxicity in fish (De Schamphelaere and Janssen, 2004, 2002; De Schamphelaere et al., 2004, 2003, 2002; Heijerick et al., 2002a, b; Di Toro et al., 2001; Santore et al., 2001; McGeer et al., 2000). The model can be used to distinguish, at least conceptually, metals that will bioconcentrate at the site of toxicity (e.g., gill or other biotic ligand) from the total metal pools in an organism and the bioavailable metal pool in the exposure media. The model also can be applied to algae (De Schamphelaere et al., 2003; Heijerick et al., 2002) and *Daphnia* (De Schamphelaere and Janssen, 2004, 2002; De Schamphelaere et al., 2004, 2002). The BLM recently has been incorporated into draft revisions to EPA's national water quality criteria for Cu (it has been used in risk assessments at a range of geographic scales), and it is being applied as an alternative to the WER approaches for setting site-specific discharge objectives. The BLM has the potential to address spatial and temporal factors that affect bioavailability, provided that the variability in water quality parameters used as inputs to the model can be quantified or predicted (e.g., pH, DOC, K^+ , Na^+ , Ca^{+2} , Mg^{+2}). However, the risk assessor should be aware of the many limitations in applying the BLM (or any Free Ion model). For example, the development of the BLM has focused primarily on bioavailability and acute exposures. Work has begun to extend the BLM to chronic toxicity for some organism/metal combinations (e.g., De Schamphelaere and Janssen, 2004; Paquin et al., 2002a, b), and further development is expected. Also, the BLM is currently based on metal uptake through the dissolved phase; thus, additional research is needed to address metal uptake and toxicity via the diet.

5.2.5.2. *Sediment Phase*

Risk assessors have several approaches for estimating exposures to sediment-associated metals that account for bioavailability differences. The equilibrium partitioning approach (EqP) assumes that chemical activity in the sediment, as indexed by chemical concentration in the interstitial water, is proportional to the chemical's bioavailability to sediment-dwelling organisms. In anoxic sediments, sulfides provide the primary binding phase for many cationic metals. These metal sulfides are highly insoluble and are thought to have very low toxicity. Thus, in sediments where there is more sulfide than metal, most cationic metals should be present as insoluble sulfides and relatively nontoxic. The amount of reactive sulfide is quantified by measuring the amount of sulfide freed when sediment is extracted with 1 N HCl. This procedurally defined quantity is known as *acid volatile sulfide* (AVS). The amount of reactive metal is determined from the same extraction by measuring the metal concentration in the acid extract. This quantity is known as *simultaneously extracted metal* (SEM). The risk assessor then can determine the potential bioavailability of a metal by comparing the relative molar concentrations of the SEM and AVS. When $SEM - AVS < 0$, sufficient sulfide exists to bind all SEM, and metal toxicity is not expected. When $SEM - AVS > 0$, metal is present beyond the binding capacity of sulfide, and toxicity may occur if there is sufficient excess metal but not sufficient other binding phases to bind the metal. Use of this SEM-AVS as exposure estimates that are correlated with toxicity of metals in sediment has been explored closely for many metals (Ankley et al., 1996, 1991; Berry et al., 1996; Hansen et al., 1996; Carlson et al., 1991; Di Toro et al., 1990).

Sediment-Associated Metals

When the molar concentrations of acid-volatile sulfide in sediment exceed the amount of simultaneously extracted metal, the metals are expected to be associated with the solid phase and not to be toxic.

However, risk assessors should be aware that although the correspondence of SEM-AVS to toxicity was found, some questions remain about the applicability of the approach to all benthic organisms because it is based on the chemistry of bulk anoxic sediment, and many organisms live in oxygenated burrows. In addition, several studies have shown some degree of metal accumulation in organisms exposed to sediments where sulfide is in excess and metals are thought to be nonbioavailable, or at least nontoxic (Ankley et al., 1996). However, the lack of toxicity observed when AVS exceeds SEM suggests that this bioaccumulated metal may not be biologically available. A better understanding of the mechanisms of metal accumulation from sediment and their relationship to toxic effects is needed to help interpret these issues. Until such information becomes available, risk assessors can use the SEM-AVS model in exposure estimations as long as its shortcomings are acknowledged appropriately and uncertainties are recorded in the Risk Characterization phase of the assessment.

Other tools risk assessors can use to determine the bioavailable concentrations of sediment-bound metals include metal concentrations in the chemical extracts (Fan and Wang,

2001; Babukutty and Chacko, 1995; Tessier et al., 1984), acid extracts (Langston, 1980; Luoma and Bryan, 1978), or biomimetic extracts (Weston and Maruya, 2002; Mayer et al., 2001; Chen and Mayer, 1998). 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, Fe 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 (Creclous et al., 1982), so normalization of sediment metal concentrations to organic carbon content has been conducted in other cases. The more readily extracted metals from sequential chemical extraction schemes tend to be the most bioavailable (Young and Harvey, 1991; Tessier et al., 1984) and have been used to estimate bioavailable metal.

5.2.5.3. *Dietary Phase*

As discussed in Section 5.2.3 (Exposure Pathway Analysis) and illustrated by the conceptual model for bioavailability (Figure 2-2), it is well established that dietary exposure to metals can result in accumulation of metals in aquatic organisms. What is less well established is the best way to express dietary exposure in a way that can be linked to potentially toxic effects (either directly to the aquatic organism or its predator). The main reason for this ambiguity is that the bioavailability of dietary metals varies widely across organisms and exposure conditions and standardized approaches are not available for predicting toxicity. The subsequent discussion elaborates on this point and provides some suggestions for how risk assessors might address dietary metals in different assessment contexts (screening vs. definitive).

Dietborne Metal Exposure

Risk assessors should consider dietborne metal exposure in two contexts: (1) dietborne exposure leading to accumulation and exposure to higher levels in the food chain (e.g., humans, wildlife) and (2) dietborne exposure leading to direct effects on exposed organisms.

After ingestion, some of the dietary metal can be released from the ingested particle into the gastrointestinal fluids of the animal (Chen and Mayer, 1999; Mayer et al., 1997; Gagnon and Fisher, 1997) and become available for assimilation into the tissues of the animal and the tissues of its consumer (i.e., trophic transfer). Assimilation efficiency (i.e., the net amount of metal retained in tissues relative to the amount ingested from food) is a common measure of the bioavailability of a chemical from food, and the risk assessor may find this to be a useful parameter for comparing the potential for toxicity among different types of organisms. Assimilation efficiency is also an important input parameter for estimating metal bioaccumulation using kinetic-based bioaccumulation models (e.g., Luoma and Rainbow, 2005). Assimilation efficiencies can vary widely depending on the metal, its form and distribution in prey, species digestive physiology (e.g., gut residence time), environmental conditions (e.g., temperature), food quality, food ingestion rate, and metal concentration in the diet. Thus, risk

assessors should consider likely ranges of assimilation efficiencies for a particular metal-animal combination when evaluating metal bioavailability from the diet. A number of reviews have summarized current knowledge of assimilation efficiencies of ingested metals among different aquatic animal species (Wang and Fisher, 1999; Fisher and Reinfelder, 1995).

The distribution and form of metals in dietary organisms is of critical importance for understanding the bioavailability of dietary metals and trophic transfer potential. For example, metals in the cytosolic fraction of phytoplankton and “soft parts” of zooplankton have been shown to correlate well with bioaccumulated metal in their predators (e.g., herbivores and plantivorous fish, respectively) (Wang and Fisher, 1996; Reinfelder and Fisher, 1994a, b). Metals sorbed to the cell wall of phytoplankton and the exoskeleton of zooplankton were poorly assimilated by consumers. The bioavailability of metal-enriched granules in prey (a detoxification and storage mechanism exhibited by some organisms) has been shown to be negligible or substantially reduced when consumed by certain predators (e.g., Wallace et al., 2003, 1998; Wang, 2002; Wang and Fisher, 1999; Nott and Nicolaidou, 1990). However, the risk assessor should be aware that the bioavailability of metal-enriched granules in prey can vary among metals and with type of granule (Wang, 2002; Mason and Jenkins, 1995; Nott and Nicolaidou, 1990) and may also depend somewhat on digestive physiology of the predator (e.g., gut pH, retention time). As a result of these findings, fractionating body burdens of metals (e.g., cytosolic metal vs. metal granules) has been suggested as a better means of identifying the bioavailable fraction of dietborne metals (Seebaugh and Wallace, 2004; Wallace et al., 2003; Fisher and Reinfelder, 1995; Reinfelder and Fisher, 1994). Although such techniques show promise for operationally defining the extent to which dietary metals may be bioavailable for trophic transfer in aquatic food webs, risk assessors should understand that broad-scale application of these techniques to metals risk assessments is presently limited by the relatively small number of metals and predator-prey relationships evaluated.

Despite the uncertainties associated with bioavailability and trophic transfer of dietary metals, the use of whole-body inorganic metal concentrations in prey species may have some utility to risk assessors for conservatively screening for exposure and potential risks to consumers (i.e., in cases where whole-body residues are below dietary toxic thresholds). For more definitive assessments, further research is needed to quantify the bioavailability and effects of inorganic dietary metals, with the exception of certain organometallics (e.g., methyl mercury) and metalloids (e.g., Se) where dietary toxicity has been well established.

Trophic Transfer

Trophic transfer is the transfer of a chemical from prey species to a predator species via dietary exposure.

Biomagnification is a type of trophic transfer where chemical concentrations increase in organisms from a lower trophic level to a higher trophic level within the same food web.

Biodilution represents a decrease in organism concentration with increasing trophic level.

5.2.5.4. *Bioaccumulation and Trophic Transfer*

Assessing and predicting the bioaccumulation of metals in aquatic ecosystems is a component of many Agency regulatory and nonregulatory activities (e.g., chemical ranking/classification, derivation of national water quality criteria, Superfund site risk assessments; see Section 2.3.1 for definitions and a conceptual model related to bioaccumulation). Interest in metals bioaccumulation originates from concerns regarding the direct impact of metals on organisms accumulating the metal and indirect impacts on their consumers (i.e., trophic transfer). Unlike certain persistent and bioaccumulative organic compounds, which tend to biomagnify in aquatic food webs (e.g., DDT/DDE, PCBs, PCDD/PCDF), inorganic metal compounds rarely biomagnify across three or more trophic levels (McGeer et al., 2004; Suedel et al., 1994); however, certain organometallics can biomagnify in aquatic food chains. Some metals (e.g., lead) tend to biodilute in aquatic food webs. Risk assessors should not interpret lack of biomagnification as lack of exposure or concern via trophic transfer (see text box). Even in the absence of biomagnification, aquatic organisms can bioaccumulate relatively large amounts of metals and become a significant source of dietary metal to their predators (Reinfelder et al., 1998).

For many nonionic organic chemicals, risk assessors can derive first-order approximations of bioaccumulation potential from information on chemical properties and organism attributes (e.g., K_{ow} and lipid content) and their use as inputs to simplified, fugacity-based models (e.g., Gobas et al., 1993). For metals, analogous methods to predict bioaccumulation based on simple chemical properties are not available or are not widely validated. The lack of analogous models for metals is likely due, at least in part, to the high degree of specificity exhibited by the mechanisms and processes underlying metals bioaccumulation (e.g., speciation, exposure conditions, and organism physiology) (see McGeer et al., 2004; Rainbow, 2002; Mason and Jenkins, 1995). As a result, risk assessors currently are limited to using an empirical approach for assessing and predicting metals bioaccumulation. Typically, this requires direct measurement of metal concentrations in the organism or experimentally-determined parameters for use as input to bioaccumulation models (e.g., gill uptake rate, elimination rate, assimilation efficiency).

Aquatic ecological risk assessors commonly use bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) to quantify chemical accumulation in tissue relative to concentration in water. BCFs and BAFs are determined as the ratio of the chemical concentration in tissue to its concentration in water (using the steady-state method) or as a ratio of uptake rate (k_u) and elimination rate (k_e) constants (using the kinetic method). Measurement of BCFs or BAFs usually is conducted for conditions that approximate steady-state (i.e., where accumulation remains relatively constant due to chemical uptake being offset by its elimination by the organism). It is assumed that the greater the BAF or BCF, the greater a chemical's bioaccumulation or bioconcentration potential.

Risk assessors should recognize that considerable uncertainty can be associated with the application of literature-derived BCFs and BAFs for assessing the risks of metals, as variability in BCFs and BAFs for metals is known to be high (e.g., 50-fold or higher within a metal). Most of this uncertainty results from bioavailability differences between the studies from which the BCF or BAF is measured and the site(s) to which it is being applied (e.g., water quality characteristics, metal speciation, exposure pathways).

Other sources of uncertainty that risk assessors should consider in the broad application of BCF/BAF data are rooted in the complex mechanisms of metal toxicokinetics (uptake, metabolism, distribution, elimination). For example, unlike hydrophobic, nonionic organic chemicals where uptake across biological membranes generally occurs via passive diffusion, the uptake of metals is believed to involve a number of specific transport mechanisms. Some of these transport mechanisms involve binding with membrane carrier proteins, transport through hydrophilic membrane channels, and endocytosis. Passive diffusion is thought to be reserved for certain lipid soluble forms of metals, such as alkyl-metal compounds and neutral, inorganically complexed metal species (e.g., HgCl_2^0). The implication of these specific transport mechanisms is that metal bioaccumulation can involve saturable uptake kinetics, such that BCFs and BAFs depend on exposure concentration. The existence of saturable uptake mechanisms, the presence of significant amounts of stored metal in organisms, and the ability of some organisms to regulate bioaccumulated metal within certain ranges are all thought to be responsible for the inverse relationship that has been frequently reported between BCFs/BAFs and metal exposure concentrations (McGeer et al., 2003; Borgman et al., 2004). In these cases, higher BCFs or BAFs are associated with lower exposure concentrations and also can be associated with lower tissue concentrations within a given BCF or BAF study. This is counter to the implicit assumption that higher BCFs or BAFs indicate higher metal hazard.

As a result of the aforementioned uncertainties, risk assessors must be careful in broad-scale application of BCF and BAF data for metals. Specifically, the current science does not support the use of a single, generic threshold BCF or BAF value as an indicator of metal hazard. Similarly for national risk assessments, use of a single BCF or BAF value holds little utility due to high uncertainty that results from differences in bioavailability, exposure conditions, and species-specific factors that influence metal bioaccumulation by aquatic organisms. When extrapolation across sites is necessary and limited data prevent application of alternative approaches (discussed below), uncertainty in the use of BCFs and BAFs can be reduced by expressing them as a function of media chemistry (i.e., to address bioavailable metal), exposure concentrations (i.e., to address concentration dependency issues), and limiting extrapolations to within a particular species or closely related species. The use of BCFs and BAFs for metals assessments appears to have most value for site-specific applications, when appropriate measurements are taken from the site(s) of interest and extrapolation of BCF/BAF values across differing exposure conditions and species is minimized.

Risk assessors should be aware of several alternatives for assessing metals bioaccumulation that address some of the concerns listed above. One of these is to develop regression relationships between tissue and exposure concentrations. Such regression relationships have been used to characterize bioaccumulation of metals by soil organisms (U.S. EPA, 2003c; Sample et al., 1999), but they have not yet been compiled for aquatic systems. The advantage of this technique is that it addresses the dependency of BCF or BAF on exposure concentration. However, it does not explicitly adjust for bioavailability differences that occur across sites. Another alternative is to use a kinetic-based model for describing bioaccumulation (Luoma and Rainbow, 2005; Wang and Zauke, 2004; Kahle and Zauke, 2003; Chang and Reinfelder, 2002; Reinfelder et al., 1998). These models can improve predictions of metal bioaccumulation in aquatic organisms because they incorporate different exposure routes (e.g., water vs. diet) and the dynamic nature of metal bioaccumulation processes. For example, Luoma and Rainbow (2005) reviewed the DYNBAM model (a single-compartment, kinetic-based bioaccumulation model) and found it to accurately predict metal bioaccumulation for a wide range of metals, organisms, and habitats based on data derived from 15 separate studies. Importantly, DYNBAM and similar such models require experimental data measured under environmentally-realistic conditions in order to derive model parameters for each metal-species combination (e.g., uptake and elimination rates, assimilation efficiency, food ingestion rates). Compilations of such data on model input parameters are available for some species and metals (e.g., Wang and Fisher, 1999, for aquatic invertebrates). Clason et al. (2004) and Kahle and Zauke (2003) have developed two-compartment bioaccumulation models for amphipod crustaceans that incorporate background metal and saturation of uptake kinetics. Currently, however, these models include only the dissolved phase and do not account for uptake from the diet.

The bioaccumulation models described above offer strong promise for improving bioaccumulation predictions in aquatic risk assessments for metals and should be considered by risk assessors. However, risk assessors should be aware of their limitations. For example, they currently do not account for differential partitioning and bioavailability of metal in organisms (see Figure 2-2). Empirical methods are being developed to predict metal compartmentalization in tissues of aquatic organisms (e.g., Wallace and Luoma, 2003; Wallace et al., 2003), but these have not been incorporated into bioaccumulation models. These models also do not explicitly address the impact of metal speciation on bioaccumulation or link bioaccumulated metal to toxic effects, although such models are under development (Paquin et al., 2002b). Regardless of the type of bioaccumulation model used, reductions in uncertainty in metals bioaccumulation assessments should be directed at achieving robust connections between the bioaccessible/bioavailable form(s) of metals in various exposure media, their accumulation, metabolism, and distribution in tissues, and the form(s) of metals that exert their toxicity directly to the organism or indirectly to its consumers.

5.3. CHARACTERIZATION OF EFFECTS

5.3.1. Essentiality

Essentiality refers to the nutritional requirements of an organism for normal metabolic function. A key difference between metals and organic chemical contaminants is that some metals are required either as macronutrients (e.g., Fe, Ca, Mg) or micronutrients (e.g., Cu, Zn, Ni) to maintain a healthy organism. Table 6-3 in Section 6.2.1 classifies the metals addressed in this Framework by their known essentiality to plants and animals.

Consideration of essentiality by the risk assessor is important for several reasons. First, the risk assessor should ensure that toxic effects thresholds calculated from an assessment are not lower than the nutritional requirements for the particular plant or animal species being evaluated. As discussed in Sections 4 and 6, the risk assessor should be aware that such elements exhibit classic bell-shaped or biphasic dose-response (or exposure effect) relationships, with adverse effects occurring at both high and low concentrations and an optimal mid-range dose or exposure (see Abernathy et al., 1993; Chapman and Wang, 1998). For aquatic organisms, information about nutritional requirements is available for many commonly tested or cultured species. Essentiality issues also impact the bioaccumulation and toxicity of metals since organisms have evolved various mechanisms to maintain homeostasis of essential metals. Such mechanisms may also impact the bioaccumulation and toxicity of nonessential metals, particularly those that share similar binding and uptake mechanisms. In these cases, accumulation is nonlinear with respect to exposure concentration, whereby greater uptake and retention of metals occurs at low concentrations and uptake rates decrease as exposure media concentrations increase. The impact of homeostatic and other mechanisms on bioaccumulation has been discussed in Section 5.2.

5.3.2. Toxicokinetics/Toxicodynamics (Toxicity Issues)

For organometallic compounds such as organo-selenium and methyl mercury, toxicity from dietary exposure has been shown to contribute substantially to ecological risk at environmentally-realistic concentrations and thus should be considered by the risk assessor when characterizing the effects of these compounds. Beyond those two organo-metal compounds, however, the importance of exposure to dietary metals is much less clear. Toxicity to aquatic organisms from dietary exposure to metals has been demonstrated where exposure is sufficiently high, although, in some cases, these concentrations are extreme (e.g., 10,000 g/g Cu) (Handy, 1993). In such cases, 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 first via other pathways (e.g., direct toxicity of waterborne metal).

In other studies, however, effects from dietary exposure have been demonstrated at relatively low exposure concentrations (e.g., zooplankton studies by Hook and Fisher, 2002,

2001a, b). This raises additional concern for metals assessment because it increases the potential for toxicologically significant exposures to occur in cases where risk via a waterborne pathway is low. However, other studies with the same organisms and metals, but somewhat different test methods, reached different conclusions regarding the significance of dietary exposure (e.g., De Schamphelaere and Janssen, 2004; Meyer et al. [in press]). Dietary exposure of aquatic organisms to metals is an active area of research, and it is likely that new data and insights will result in a more comprehensive understanding of dietary effects. Until that time, risk assessors should make decisions regarding potential risks of dietary metal exposure on a case-by-case basis.

5.3.3. Metal Mixtures

Mixtures of metals (including metalloids and organic substances) are commonly encountered in the natural environment as a result of anthropogenic inputs and should be considered by the risk assessor for all assessments. Metal interactions, according to Calamari and Alabaster (1980), occur at three levels:

- Chemical interactions with other constituents in the media
- Interactions with the physiological processes of the organism, and
- Interactions at the site of toxic action.

The joint action of metal mixtures may be expressed in different ways, including increasing or decreasing the toxicity relative to that predicted for individual components. As a result, the toxicity of metal mixtures has important consequences for metals risk assessments. For example, toxicity has been observed for mixtures of metals present individually at nontoxic levels (e.g., at levels corresponding to water quality guidelines) (Enserink et al., 1991; Spehar and Fiandt, 1986). Despite the importance of considering the effects and mixtures of metals to aquatic organisms, risk assessors will find that predicting the toxicity of metal mixtures has proven to be a difficult challenge in aquatic toxicology.

Much of the difficulty in predicting the toxicity of metal mixtures to aquatic organisms results from differences in the bioavailability and/or methods used to define the bioavailable fraction among toxicological studies and subsequent ambiguity in interpreting mixture toxicity data. As discussed in Chapter 2, the bioavailability of metals depends on a suite of factors that can affect their speciation, complexation with ligands, and interaction with biological systems (e.g., pH, DOC, inorganic anions, and cations). Apart from bioavailability differences, the joint action of metal mixtures to aquatic organisms (i.e., antagonism, additivity, synergism) has been reported to depend on other aspects of toxicity test design, including the degree of toxicity associated with the overall mixture concentration (Mowat and Bundy, 2002; Fargašová, 2001; Herkovits et al., 1999; Spehar and Fiandt, 1986), the relative proportion of constituent

concentrations (Norwood et al., 2003; Sharma et al., 1999), the duration of the exposure (Marr et al., 1998), and several other factors related to experimental design (Norwood et al., 2003). In a similar review, the European Centre for Ecotoxicology and Toxicology of Chemicals concluded that the acute and chronic toxicity to aquatic organisms of mixtures of metals could not be reliably predicted or generalized although they recommended that, in the interim, assuming additive effects is likely “a balanced approach” for acute toxicity of metal mixtures (ECTOC, 2001).

Given these difficulties in evaluating mixtures effects, risk assessors commonly use two simplifying models: concentration addition and effects (response) addition. These models are used to classify the combined effects of chemical mixtures as being antagonistic, additive, and synergistic (also referred to as “less than additive,” “strictly additive,” and “more than additive,” respectively). Both models use metal concentrations in media to generate concentration-response curves for individual metals, and these data are then used to generate specific critical concentrations for mixture models. In the concentration addition model, all metals in a mixture are added together to predict toxicity; differing potencies are taken into account by converting chemical concentrations to an equitoxic dose, such as toxic units (TUs) or toxicity equivalence factors (TEFs), which converts all metals to one metal concentration. Concentration addition is often used when the constituents are known or assumed to act through the same or similar MOA. However, risk assessors should be aware that applying the concentration addition model to mixtures containing many metal constituents (particularly those well below toxic levels) can result in an upward bias in predicted mixture toxicity (Newman et al., 2004).

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. The effects addition model is used when constituents act or are assumed to act independently (i.e., different MOAs). Thus, the risk assessor defines the nature of the metals’ joint action (i.e., independent or similar MOA) to decide when to apply either the concentration addition or effects addition model. The risk assessor should consult information on the MOA, capacities to act as analogues for other metals, essentialities, and ligand binding tendencies to choose among these types of models.

The assumption of additivity has some regulatory precedence for use when addressing the toxicity of mixtures although not necessarily for metals. For example, the concentration addition approach is recommended for use by Australia and New Zealand for evaluating whether a mixture of less than six constituents exceeds their water quality guidelines (ANZECC and ARMGANZ, 2000). Similarly, additivity is assumed by EPA when evaluating the combined *acute* toxicity of multiple toxic effluents on the basis of whole-effluent toxicity data (U.S. EPA, 1991). Additivity is not assumed for *chronic* exposures due to lack of supporting data. For predicting the direct toxicity of mixtures of cationic metals in sediments to benthic organisms, EPA uses the \sum SEM-AVS approach described previously (see Section 5.2.5 Toxicokinetics and Toxicodynamics (Bioavailability and Bioaccumulation)). Note, however, that this method is

limited to six cationic metals (Cd, Cu, Pb, Ni, Ag, and Zn). Furthermore, this method is considered a “no effect guideline,” whereby the absence of toxicity can be predicted reliably (when $\sum SEM < AVS$) but the occurrence of toxicity (when $\sum SEM > AVS$) cannot be because of other factors that are not accounted for, which reduce metal toxicity.

Risk assessors should also consider the QICAR approach (described in Section 3.1.1) for addressing the toxicity of metal mixtures. 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 develop a model of joint independent action (Finney, 1947). They predicted that the joint action of combined metals will increasingly deviate from independent action as their ligand-binding chemistries become more and more similar. Although Microtox is considered to be a useful tool for organic contaminants, its sensitivity for evaluating metal toxicity has been called into question (Willemson et al., 1995).

It is possible that receptor binding models (e.g., FIAM) may be expanded in the future to include mixtures. In theory, if two metals compete for binding to the same site of toxic action, it should be possible to model the total metal bound to that site and, hence, to predict metal toxicity using a mechanistic receptor binding approach in an effects addition model. Alternatively, if two metals do not compete for the same binding site, then these models may provide more reliable estimates of individual metal bioavailability, which then can be combined in more accurate effects addition models. However, at present, these possibilities remain theoretical. Furthermore, this approach, while improving the ability to assess the effects of metal mixtures, does not include temporal aspects (i.e., “time-to-response” versus concentration).

From the preceding discussion, it should be clear that the accurate prediction of the joint toxicity of metal mixtures to aquatic organisms remains a significant challenge for the risk assessor. For site-specific assessments, risk assessors are encouraged to assess mixture toxicity using *in situ* measurements (i.e., bioassays using site water or sediments). This approach is the foundation of the WER procedures used by EPA for making site-specific bioavailability adjustments to metals criteria. For site-specific assessments involving sediments, risk assessors should consider using the $\sum SEM$ -AVS approach as a no-effect threshold. For national-level assessments, there is some precedence for assuming additive toxicity of mixture constituents, particularly when considering acute effects. However, the risk assessor should carefully consider the limitations to assuming strict additivity (i.e., potential for overprediction or underprediction of toxicity) and highlight these uncertainties in the Risk Characterization phase of the aquatic risk assessment.

5.3.4. Critical Body Residues

The bioavailability of metals from multiple exposure routes (water column, food, sediments) should be considered in aquatic risk assessments to account for relative contributions to overall toxicity. In concept, expressing toxicity on the basis of tissue residues is an attractive

approach to accomplishing this because it integrates chemical uptake from different routes of exposure, accounts for differences in bioavailability from exposure media, and addresses differences in toxicokinetics that occur for different species.

Expressing toxicological effects on the basis of internal (tissue) concentrations (e.g., use of critical body residues [CBR] or residue-response relationships) has gained significant attention in the aquatic ecotoxicology literature, particularly for organic chemicals (e.g., Landrum et al., 2005, 2004; Escher and Hermens, 2002; McCarty and Mackay, 1993; Cook et al., 1993, 1989; McCarty, 1986; Veith et al., 1983; Könemann, 1981). For many nonionic organic chemicals, available data indicate that whole-body burdens of chemical (normalized to lipid content) can serve as useful metrics of toxicological dose, and these relationships appear to be independent of whether exposure was via water or diet. A major strength of the CBR approach for organic chemicals is that it effectively integrates different exposure pathways into a single expression of dose and toxicological potency.

For metals (aside from organo-selenium and methyl mercury), the situation is far more complex and the CBR approach does not appear to be a robust indicator of toxic dose. One reason why the CBR approach currently appears more limited for metals relates to differences in their mechanisms of uptake, distribution, and disposition in aquatic organisms. Specifically, the distribution of nonionic organic chemicals in organisms is largely influenced by passive partitioning. In contrast, the uptake, distribution, and disposition of metals are typically governed by highly-specific biochemical processes that alter the metal form and involve facilitated or active transport. 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. As a basis for improving residue-response relationships, 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 (Wallace and Luoma, 2003; Wallace et al., 2003; Wallace and Lopez, 1996).

Other researchers have suggested that CBR relationships are confounded because the factor that determines the effects is not whole-body concentration per se, but the *rate* of metal uptake in relation to metabolic capacity for detoxification and storage; therefore, the effects are governed by factors that influence the rate of uptake. When uptake rate is elevated, the concentration of metabolically active metal at the site(s) of action increases (e.g., the spillover hypothesis) and effects ensue (Rainbow, 2002). Because different species of aquatic organisms invoke different “accumulation strategies” (i.e., involving combinations of regulation, detoxification, and storage), considerable difficulties arise among species when interpreting the toxicological significance of metal whole-body residues.

Therefore, risk assessors should ensure that a toxicologically valid residue-response relationship supports the CBR threshold before using tissue residues as indicators of toxicity.

Although many toxicological studies report measurements of metal residues in multiple tissues along with adverse effects, these tissue residue values may not be appropriate for use as a CBR threshold because metal concentrations in some tissues may have little or no relationship with toxicity. Furthermore, risk assessors are cautioned against extrapolating CBRs across differing exposure routes (food vs. water), durations, tissues, or species, because the potency of metal residues often differs depending on these factors.

5.3. RISK CHARACTERIZATION

As described in Section 2.4, Risk Characterization is the final phase of the risk assessment and is the culmination of the Planning, Problem Formulation, and Analysis of predicted or observed adverse effects. Risk Characterization produces a detailed description of the risk estimate(s), evaluates and summarizes the lines of evidence that support or refute the risk estimate(s), describes the uncertainties, assumptions and qualifiers in the risk assessment, and reports the conclusions of the assessment to risk managers (U.S. EPA, 2000c, 1998a).

While there are no metal-specific methods in the Risk Characterization, there are aspects that are important to metals risk assessments. For example, considering multiple lines of evidence such as results from *in situ* toxicity testing or biological assessments can be valuable for supporting the conclusions of a risk assessment. Care should be taken, however, to evaluate and present the limitations associated with each line of evidence, as discrepancies may not always indicate underlying differences; rather, they may reflect inherent limitations of each of the methods. For example, biological assessment methods may not be sufficiently sensitive to detect the level of effects or exposures that are of concern in the risk assessment. Documenting assumptions and uncertainties (e.g., use of background metal concentrations rather than added metal or specific metal species) becomes increasingly important the closer hazard thresholds are to background concentrations. Risk assessors also should document all assumptions and uncertainties in the methods used, such as how metals bioavailability was addressed. Because data may not be adequate to conduct a quantitative uncertainty analysis, risk assessors should describe the *sensitivity* of the risk assessment results to key assumptions and the *direction of bias* introduced by these assumptions (i.e., under- or overestimation of risks). This is particularly important for national or regional assessments, where results often are intentionally based on organisms and conditions that enhance exposure, bioavailability, and toxicological sensitivity. For essential metals, risk assessors should describe the relationship of the risk threshold to nutritionally required levels for the organisms of concern. Risk assessment results that fall below nutritionally required levels are an indication that some methods or assumptions require additional refinement. Risk assessors should carefully document the form(s) of metals used in the exposure and effects assessment, as they frequently differ due to data limitations. Additional issues and questions that should be addressed in the risk assessment are listed in Section 2.4.

6. TERRESTRIAL ECOLOGICAL RISK ASSESSMENT FOR METALS

This section of the Framework provides an overview of how the principles for metals risk assessment apply to ecological risk assessments for terrestrial environments. Receptors typically considered in these assessments include soil invertebrates, plants, and wildlife species. Some assessments also examine effects on microbiota and soil processes. This section of the Framework builds on the information presented in Chapter 2 that lays out issues to be considered during Problem Formulation and that describes metal chemistry associated with soil systems. That information is not repeated here and the reader should refer to Chapter 2 for this information.

6.1. METALS PRINCIPLES

Metals have specific environmental and biotic attributes that should be considered in all risk assessments. These principles for metals risk assessment (see Chapters 1 and 2) apply in various ways to ecological risk assessments depending on the scale of the assessment (site specific, regional, or national). This section describes applications of the principles to terrestrial ecological assessments within the standard risk assessment framework. Specifically, they fall into the risk assessment paradigm as follows:

Background levels	Exposure Assessment
Mixtures	Exposure and Effects Assessment
Essentiality	Effects Assessment
Forms of metals	Exposure and Effects Assessment
Toxicokinetics/toxicodynamics	Exposure Assessment (bioavailability) and Effects Assessment (ADME and toxicity)

6.2. CHARACTERIZATION OF EXPOSURE

Metal exposure assessment includes characterization of the exposure routes and pathways specific to metals, the 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.

6.2.1. Natural Occurrence of Metals

At a national level, metal concentrations vary naturally in soils across the U.S. These variations pose challenges for conducting national assessments of risk to terrestrial ecological receptors. The assessor may decide to use a single toxicity level regardless of background concentrations for a screening type assessment (see text box on ecological soil screening levels or Eco SSLs) (U.S. EPA, 2003c) or may prefer to divide the country into regions of similar metal

background levels (metalloregions). Exposure assessments should consider metal levels inclusive of background.

At the regional and local (site) scales, risk assessors should account for the natural occurrence of metals either at the beginning of an assessment (i.e., during Problem Formulation), during the assessment, or when making risk management decisions about the implications of the predicted or observed levels of metals in soils. Because the national soil survey⁴ is over 20 years old, risk assessors should consider the feasibility of generating site-specific concentrations for local risk assessments.

EPA's Ecological Soil Screening Levels

EPA's **Ecological Soil Screening Levels** (Eco SSLs) for metals are national-level concentrations of metals in soils that are protective of wildlife, plants, and soil organisms. These values are lower than naturally occurring levels in some parts of the country. Exceedences of such levels does not mean that a risk exists but does mean that a more regional or site-specific assessment may be needed.

More appropriately, risk assessors should avoid single-result assessments for the entire country. 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 water quality criteria (Griffith et al., 1999). The use of metalloregions provides the ability to account for the broad regional parameters affecting metal availability in soils and waters as well as for the differences in organism response to added metal.

The metalloregion concept (McLaughlin and Smolders, 2001), although intuitively appropriate, has not yet been fully developed for the U.S. The country has been divided into ecoregions for both aquatic and terrestrial systems (Bailey et al., 1994; Bailey, 1983). These 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 Web site at <http://www.epa.gov/wed/pages/ecoregions/ecoregions.htm>). To complete the metalloregion concept, soil properties that affect bioavailability (e.g., pH, cation exchange capacity [CEC], and organic matter [OM]) should be overlaid on the ecoregions, along with soil type (e.g., sandy loam, clay loam) and background concentrations 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. Nevertheless, work is under way to develop metalloregions (e.g., McLaughlin and Smolders, 2001), although it is likely to be several years from the time of this writing before they are available for use in a decision-making capacity.

⁴ Schacklette, HT; Boerngen, JG. (1984). Element concentrations in soils and surficial materials of the conterminous United States. U.S. Geological Survey Professional Paper 1270. 105 pp.

6.2.2. Forms of Metals

The physical and chemical forms of metals influence exposure and subsequent effects and can be influenced by physical/chemical conditions in the environment. National level assessments involve a broad range of environmental conditions and so the risk assessor should account for different metal species in different locations and soil types. As assessments transition from national, to regional, to local, the assessor should incorporate site-specific soil parameters that influence metal speciation (e.g., pH, CEC, clay content). National values (e.g., geometric mean values) of these parameters should be used, with the same recommendation as discussed in Section 5.1.3 on Natural Occurrence of Metals.

6.2.3. Exposure Routes

The major metal *exposure route* that the risk assessor should consider for wildlife is ingestion, with a minor (and often unknown) inhalation component. For plants, root uptake is the most important with leaf exposures secondary, with the exception of Hg where the majority is accumulated via foliar uptake; Cd and sometimes Pb also may be accumulated through foliage but amounts relative to soil exposure will vary depending upon soil conditions (e.g., pH). Plants may also lose metals through foliar leaching during precipitation events although to a significantly lesser extent than for other micronutrients such as potassium. Soil invertebrates are assumed to be exposed through direct contact. *Pathways* describe transport of the contaminant in the environment and include uptake and bioconcentration (e.g., dietary ingestion of a soil contaminant that has been taken up by plants). Principles of metal transport and fate in soils are applicable to assessments of risk to all terrestrial organisms and will be discussed first. However, because of significant differences in exposure routes and pathways between invertebrates, plants, and wildlife, it is more convenient to discuss exposure assessment methods by receptor group.

6.2.4. Soil Transport and Fate Models

Risk assessors routinely use transport and fate models (i.e., a computational model) to describe and quantify exposure pathways. Models are also useful in situations where risk assessors are trying to estimate exposure levels that are expected to result from the implementation of some permitting action or remediation measures at local, regional, or national scales. Numerous models are available for use; most are based on the same fundamental principles: metals are ubiquitous in the environment and within each media compartment they are present in association with water (freely dissolved metal or as organic and inorganic metal complexes),

Pathway of Exposure for Terrestrial Organisms

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).

particles (sorbed, precipitated, or incorporated within a mineral phase), and air. The risk assessor can find a more detailed discussion of these processes in Section 3.2 on Fate and Transport. Currently, there is no single model available that encompasses all the desirable metal-specific features for terrestrial systems. Discussions of the available terrestrial transport and fate models, as well as a number of chemical equilibrium models, may be found in Allen (2002).

6.2.5. Toxicokinetics/Toxicodynamics

Target organ exposure levels and subsequent effects depend on how environmental conditions affect speciation of a metal (e.g., whether an organism actively takes up or excludes metals in soils and how an organism processes metals internally). See Section 3 for details on environmental chemistry and issues relating to bioaccumulation. Risk assessors should specifically address bioavailability and bioaccumulation for each metal of concern in each environment (either a local site for site-specific assessments or some larger estimate for regional and national level assessments).

6.2.5.1. Bioavailability

Risk assessors should adjust bulk soil metal concentrations by appropriate bioavailability factors to achieve comparable, actual uptake of metals by soil organisms. This will standardize exposure values across soil types and allow for more accurate comparisons with laboratory toxicity data. Cation exchange capacity (CEC) recently has been shown to be an important factor modifying zinc bioavailability in soils, and presumably it will be important for other cationic metals as well. However, CEC is strongly dependent on the type and amount of organic material (OM) and oxyhydroxides present in the soil, and is strongly pH dependent. Surface charge on OM and oxyhydroxides increases with pH, thereby increasing their sorptive capacity for metals (thus decreasing metal bioavailability). Conversely, positive surface charges increase as the pH drops, which increases sorption of anions (e.g., As or Se) under low pH conditions and decreasing sorption of cation ionic metals. Clays, on the other hand (except for kaolinite), have a surface charge that is largely independent of pH. Therefore, normalization of toxicity data to CEC can be done only within specific soil types and pH ranges, which frequently are not specified either in laboratory bioassays or many field studies. Furthermore, it is important for the risk assessor to note that most published values of CEC are measured at pH 7. In general, risk assessors can assume that cationic metals are more bioavailable at lower soil pH (<6) and less bioavailable at higher soil pH (>8). The opposite assumption holds for anionic metals.

Soil chemical models are being developed to predict how aging will modify bulk soil concentrations when soils are amended with soluble salts. Aging reduces the bioavailable fraction of metals over time. Preliminary studies suggest that consideration of aging may result in estimates of the bioavailable fraction as low as $0.1 \times$ bulk soil concentrations (McLaughlin et

al., 2002). Until the data become available for metals of concern, toxicity values derived from soluble-salt amended soils (which have not simulated aging) cannot be reliably corrected to approximate aged metals in field situations and the risk assessor should acknowledge this as a significant uncertainty during the risk characterization.

Ideally, exposure should be expressed on the basis of pore water concentration, to account for all factors influencing bioavailability; however, there are currently significant limitations to collecting and interpreting metal-related data from soil pore waters and such information generally is not available (even at site-specific assessments and never for regional or national assessments). The risk assessor could estimate metal concentration in soil pore water using EqP theory (as with sediment pore water analyses; see Section 3.1.5). The risk assessor can use published soil binding coefficients (K_d s) to estimate partitioning between soil particles and pore water although these values also are inherently uncertain (published value depends on derivation method, soil type, etc.). Furthermore, toxicity threshold values generally are provided as bulk soil concentrations so the risk assessor would not be able to compare pore water exposure with any effects estimates.

6.2.5.2. Bioaccumulation

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 stresses 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 or soil invertebrates, the bioaccumulation factor (BAF; or biota-soil accumulation factor, 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).

Risk assessors should be aware that data applicability is directly related to which tissue is sampled and how it is processed. BAFs for plants include metals aeri ally 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 soils versus laboratory studies using the filter paper substrate protocols. Furthermore, BCFs within earthworms may not include additional feeding of the animals during the study. Field studies are reflective of chronic exposures, whereas BCFs may be calculated from shorter time frames. Ideally, risk assessors should select BCFs reported at equilibrium (i.e., after sufficient exposure time to maximize the BCF). Whole-body BAFs generally are not calculated for birds and mammals, except for small mammals such as rodents (Sample et al., 1998b). Risk assessors should understand the conditions under which metal concentrations were measured and critically examine data to determine whether they are reported

as wet or dry weight (the ratio of tissue to soil concentrations must be done on the same wet/dry weight basis for both).

For soil invertebrates and most plants, metal BAFs are typically less than 1 and usually are based on the total metal in soil and tissue that do not account for bioavailability differences. The risk assessor might consider using 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 or weak salt extractable) for expressing a BAF to allow comparison among different soils, although, in general, data are lacking for using this method.

Furthermore, the risk assessor is reminded that bioaccumulation of metals is not a simple linear relationship. Uptake is nonlinear, increasing at a decreasing rate as medium concentration increases. Models for predicting metal bioaccumulation by soil invertebrates are primarily statistical in nature, describing relationships between metal body burdens in oligochaetes and collembola, soil metal concentrations, and soil physical/chemical characteristics. Sample et al. (1998a) 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 risk assessors can use as a first approximation for bioaccumulation in soil invertebrates; however, these models are not specific to soil type and, therefore, do not account for bioavailability factors. Furthermore, they do not adequately predict Cr or Ni uptake. An alternative approach that the risk assessor could consider is the use of multivariate statistical models to look for patterns of uptake of multiple metals to predict the potential bioconcentration of one metal of particular interest (Scott-Fordsmand and Odegard, 2002) or BAF as a function of soil characteristics (Saxe et al., 2001; Peijnenburg et al., 1999a, b). 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 (Bradham, 2002; Basta et al., 1993).

The absolute level of metal accumulation is not as important as the rate of uptake (Hook and Fisher, 2002; Hook, 2001; Roesijadi, 1992). 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., metallothionein) could be exceeded; cytosolic metal levels then become unacceptably high, and adverse effects can ensue. Because measures of uptake rates are not available, static concentrations are used; the risk assessor should acknowledge this uncertainty during the Risk Characterization.

6.2.6. Soil Invertebrate Exposure

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. However,

the risk assessor should estimate exposure as a function of soil concentration, rather than as a detailed analysis of movement of metals through the food web, to generate data that will be comparable to effects concentrations. This is a reasonable approximation for soft-bodied invertebrates (e.g., earthworms) whose metal exposure is primarily through soil pore water (from both dermal absorption and soil ingestion) (Allen, 2002). There is more uncertainty in correlating soil metal concentrations with effects in hard-bodied invertebrates because they are primarily exposed through ingestion of food and incidental amounts of soil (Sample and Arenal, 2001). Regardless, risk assessors should estimate soil invertebrate exposure on the basis of total metal concentration in bulk soils (adjusted for relative bioavailability, where possible) collected in the top 0-12 cm of soil (U.S. EPA, 2003c, 1989b). In detailed, site-specific 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).

6.2.7. Plant Exposure

Plants access metals through the pore water although mycorrhizae, protons, and phytosiderophores released by the root can significantly influence the microenvironment and change uptake rates of metals (George et al., 1994; Sharma et al., 1994; Laurie and Manthey, 1994; Arnold and Kapustka, 1993). 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, or whether it is mistaken for an essential micronutrient. Plants can be exposed to metals via aerial deposition onto leaf surfaces, trapping metals in hairs or rough cuticular surfaces. This might provide an exposure route for herbivores; it may also provide an exposure route for plants, as there are ion channels through the cuticle that are able to transport ionic metals from the leaf surface to other locations in the plant, depending on the inherent mobility of the metal in the xylem and phloem (Marschner, 1995).

The risk assessor should consider the default approach to estimating exposure of plants to metal as measuring metal concentrations in bulk soil (top 0-12 cm). However, as with soil invertebrates, this overestimates exposure because it does not account for differential bioavailability and aging. The risk assessor generally can categorize metal bioavailability and uptake based on soil pH and organic matter (see Section 3.1.6.5). 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).

Table 6-1. Qualitative bioavailability of metal cations in natural soils to plants and soil invertebrates

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	Very high	High	Medium
5.5 < Soil pH ≤ 7	High	Medium	Low
7 ≤ Soil pH ≤ 8.5	Medium	Low	Very low

Table 6-2. Qualitative bioavailability of metal anions in natural soils to plants and soil invertebrates

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 (2003c).

Qualitative relationships between soil chemistry and bioavailability are appropriate for national-scale application. However, for site-specific or metals-specific applications, the risk assessor should use quantitative methods. Parker and Pedler (1997) and Lund (1990) have suggested that only uncomplexed, free ionic species of cations can be taken up by roots, and this has been described using a Free Ion Activity Model (FIAM) similar to the Biotic Ligand Model (BLM) used in aquatic systems. However, significant exceptions to the free-ion model have been identified; so until this theory is tested more thoroughly, the risk assessor should continue to estimate exposures using bulk soil values with qualitative estimates of bioavailability based on soil type (pH and OM). Again, the risk assessor should acknowledge these uncertainties during the Risk Characterization.

6.2.8. Wildlife Exposure

The relative importance of exposure pathways and routes varies by animal species and by metal, although, in general, wildlife exposure is primarily through diet and incidental ingestion

of soils or sediments. There are certain chemicals and exposure situations for which inhalation or dermal pathways are important, but in most situations the risk assessor can consider them to be insignificant contributors to total metal loads (U.S. EPA, 2003c).

<p style="text-align: center;">Exposure Pathway for Terrestrial Wildlife</p> <p style="text-align: center;">Food and the incidental ingestion of soil are the two most important exposure pathways for terrestrial wildlife.</p>

Wildlife food chain exposures for metals are controlled by bioavailability, bioaccessibility, and bioaccumulation. Bioaccessibility of metals to animals and plants that live on or in the soils can be influenced by soil parameters, such as pH, CEC, and organic carbon. These soil parameters tend to be less important for soils that are incidentally ingested by wildlife species.

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. In the absence of site-specific information, the risk assessor can use the following generalizations to determine the relative importance of incidental soil ingestion versus dietary metals:

1. Incidental soil ingestion is a proportionally more important pathway for herbivores than for carnivores or invertivores.
2. 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*.)
3. If bioaccumulation is low ($\ll 1$), importance of soil ingestion versus diet for metal exposure increases.
4. When bioaccumulation is greater (~ 1 or higher), the food pathway should dominate.
5. The closer the association an animal has to the ground, the greater the importance of soil ingestion. This association may be due to ground foraging, burrowing habits, etc.
6. The looser the association with the ground (e.g., piscivores, aerial/arboreal insectivores, raptors), the lower the importance of soil ingestion.

Figure 6-1 provides a simple scheme for the risk assessor to use for judging the relative contribution of food and soil before accounting for bioavailability. The assessor should assume that incidental ingestion of soil becomes proportionally more important for exposure to wildlife when (1) the bioaccumulation factor (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%. However, the risk assessor should use these generalizations with caution for site-specific assessments. As the risk assessor acquires more site-specific information, 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. Therefore, when the exposure is being driven by incidental soil ingestion, the risk assessor should consider refinements of exposure estimates through a better understanding of bioavailability, although very little information is available on this for most wildlife species.

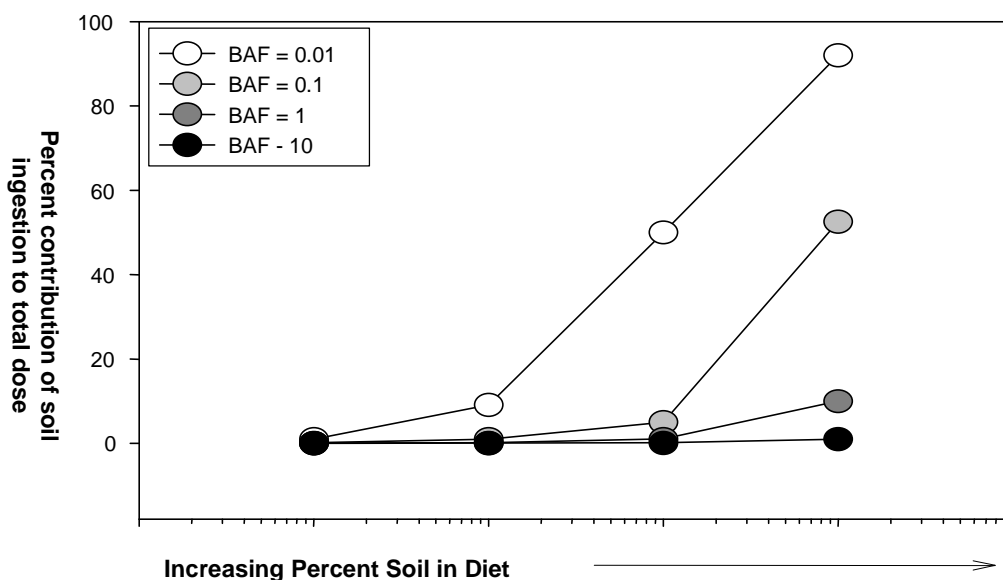


Figure 6-1. Generalized representation of percent contribution of incidental soil ingestion to oral dose for wildlife at different soil ingestion rates and bioaccumulation factors and a bioavailability of 100 percent.

The risk assessor should be cautious about extrapolating bioavailability adjustments for wildlife from models developed for estimation of bioavailability of metals in soils for incidental human exposures. There are significant variations in digestive physiology and anatomy across mammalian and avian species that alter the degree of assimilation and uptake of metals (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.

Food chain modeling can be used to estimate the exposure of wildlife to metals based on the ingestion of soil, food, and water. The risk assessor should use the same dietary uptake

model for metals as is used for organic substances, e.g., Eco SSLs; Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) (Sample et al., 1997; U.S. EPA, 1997d). For national or regional risk assessments, the assessor may use trophic transfer rates to model food concentrations but only on the basis of soil measurements (rather than using direct measures of concentration of metals in food items). As with aquatic organisms, trophic transfer values for metals in terrestrial systems are an inverse function of soil concentrations. Therefore, the risk assessor should not use constants for this term but rather should generate regression equations of plant and invertebrate uptake rates as a function of soil concentrations and use which ever value(s) that are consistent with the degree of conservatism or amount of realism appropriate for the assessment. Sample et al. (1998a) developed uptake models to predict concentrations in earthworms from soil concentrations and Efroymsen et al. (2001) provides similar information for plants (see Section 6.5.2.3 Bioaccumulation for a more detailed discussion).

With the exception of a few hyperaccumulator species, the risk assessor can reasonably assume that most plant species do not bioconcentrate metals (i.e., BAFs <1). Pb, As, Cr, and Co are not taken up by plants in measurable quantities, and the small amount that is taken up is mostly confined to root tissues (Chaney et al., 2000; McGrath, 1995; Chaney and Ryan, 1994; Xu and Thornton, 1985). In contrast, many plants are quite sensitive to some metals (Mn, Zn, Cu, for example); the risk assessor should be aware that plants frequently die before achieving high metal concentration levels that pose a threat to animals via food chain transfer (with the exception of the hyperaccumulator species, as noted above).

6.3. CHARACTERIZATION OF EFFECTS

When assessing metal toxicity to terrestrial organisms, the risk assessor should understand both the natural mechanisms of 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. The risk assessor should also consider interactions between metals in either their uptake or toxicity (such as Cd/Ca/Zn, Hg/Se, Cu/Mo). Risk assessments for metals are further complicated by the need to express the dose-response (or concentration-response) functions in bioavailable units that are functionally equivalent to measures of exposure. This section provides tools and approaches risk assessors can use when addressing issues of essentiality, metal mixtures, and appropriate use of toxicity tests; issues of how acclimation or adaptation to continued exposures may affect toxicity have been addressed in Sections 1.4.1 and 4.2.1 on Natural Occurrence of Metals.

6.3.1. Essentiality

<p style="text-align: center;">Essentiality</p> <p>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.</p>

Essentiality, or the requirement for normal organism metabolic function, of some metals is one of the primary factors that differentiates risk assessment for metals and metal compounds from that of synthetic organic chemicals (Janssen and Muysen, 2001). Some trace elements, such as Co, Cu, Fe, Mn, Se, Mo, and Zn, are necessary for the normal development of plants and animals. Other metals, such as As, Cd, Pb, and Hg, have no known functions in plants and animals (Mertz, 1981). Table 6-3 classifies the metals addressed in this Framework by their known essentiality to organisms.

The risk assessor should be sure 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. If TRVs are set too low (i.e., in the range where deficiency can occur), the determination of risk will be erroneous and deficiency effects will be mistaken for toxic responses. For wildlife, the risk assessor can consult the literature on dietary requirements of essential elements for livestock (McDowell, 2003; NAS/NRC, 1994a, 1980). Marschner (1995) summarizes the minimum concentrations required for plant growth.

Because of differences in test conditions among published studies, it may be difficult for the risk assessor 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. Furthermore, addition of safety factors when deriving protective values often results in concentrations significantly below required intake. The risk assessor should address these and similar uncertainties in toxicity threshold derivations as part of the Risk Characterization process. Detailed site-specific assessments, where more accurate estimates of effects thresholds are expected, may require the risk assessor to request additional bioassays to characterize the biphasic dose-response curve and determine both required and excessive threshold levels.

Threshold Values

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, for the risk assessor 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 can be used by the risk assessor, if they are not lower than estimated requirements. Detailed, higher level assessments may require additional bioassays to characterize the biphasic dose-response curve and determination of both required and excessive threshold levels.

Table 6-3. 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 (Mn)	X	x			
Mercury (Hg)					x
Molybdenum (Mo)	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 NAS/NRC (1980) and Barak (1999). Fairbrother and Kapustka (1997) discussed the roots of essentiality of naturally occurring elements.

6.3.2. Toxicity Tests

For assessments conducted for regional or national assessments, criteria development, or ranking purposes, risk assessors should acknowledge that results will be based on organisms and soil types that result in greatest bioavailability and sensitivity. The risk assessor should take great care to ensure that the organism-environment combinations that are assessed are, in fact,

compatible with real-world conditions. 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, risk assessors could use data from standard test species and conditions, but uncertainty factors may be warranted to adjust the final toxicity value.

6.3.3. Metal Mixtures

Mixtures of metals (including metalloids and other contaminants) are commonly encountered in the natural environment as a result of anthropogenic inputs and should be considered by the risk assessor for all assessments. 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, and
3. Interactions at the site of toxic action.

The joint action of metal mixtures may be expressed in different ways, such as increasing or decreasing the toxicity relative to that predicted for individual components. As a result, the toxicity of metal mixtures has important consequences for metals risk assessments. However, predicting the toxicity of metal mixtures has proven to be a difficult challenge in ecotoxicology.

Much of the difficulty in interpreting the available information on the toxic effects of metal mixtures is due to differences in the bioavailability of metals (and measures used to define the bioavailable fraction) that occur across mixture studies. As discussed in Section 3, the bioavailability of metals depends on a suite of factors affecting their speciation, complexation with ligands, and interaction with biological systems. Nevertheless, the risk assessor needs some measure of the bioavailable metal fraction in the exposure media to accurately predict the effects of metals mixtures (Sauvé et al., 1998; Weltje, 1998; Posthuma et al., 1997). Besides bioavailability issues, the joint action of metal mixtures can depend on the overall mixture concentrations and the relative proportion of the constituent metals, as has been seen in aquatic studies (Norwood et al., 2003; Mowat and Bundy, 2002; Fargašová, 2001; Sharma et al. 1999).

The two most common classes of models used to predict mixture toxicity are the Concentration Addition and Effects Addition models. These models have been used to classify the combined effects of chemical mixtures as being *less than additive* (i.e., when the observed effect is less than the model prediction), *strictly additive* (i.e., matching model predictions), and *more than additive* (i.e., when the observed effect is greater than model predictions; Norwood et al., 2003). Both models use metal concentrations in media to generate concentration-response curves for individual metals, and these data are then used to generate specific critical concentrations for mixture models. In the Concentration Addition model, all metals in a mixture are added together to predict toxicity; differing potencies are taken into account by converting

chemical concentrations to an equitoxic dose (e.g., Toxic Units (TUs) or Toxicity Equivalence Factors (TEFs), which converts all metals to one metal concentration). Concentration Addition is used often when the constituents are known or assumed to act through the same or similar MOA. However, the risk assessor should use caution when applying the Concentration Addition model to mixtures containing many metal constituents (particularly those well below toxic levels) because of the potential for an upward bias in predicted mixture toxicity (Newman et al., 2004). In the Effects Addition model, differing potencies are ignored, and the effect of each metal's concentration is combined to predict mixture toxicity. The Effect Addition model is often used when constituents act independently (i.e., different modes of action). Only the Concentration Addition model allows detection of toxicity that is more than additive. Thus, a key issue in applying either the Concentration Addition or Effects Addition model is to define the nature of the metals' joint action (i.e., independent or similar mode of action). The risk assessor can use information on the MOA, capacities to act as analogues for other metals, essentialities and ligand binding tendencies to make this decision.

Risk assessors should keep in mind, however, that toxicities of certain metal elements are associated with deficiencies of others. For example, increased Zn, Cu, and Ni toxicities can be associated with Fe deficiencies (Bingham et al., 1986), and increased Pb and Zn toxicities can also be related to P deficiencies (Brown et al., 2000, 1999; Laperche et al., 1997). The behavior of plant species in response to nutrient deficiencies varies, and this behavior can affect the uptake of metal elements (Marschner, 1998). Similar interactions occur in wildlife; for example, Cu toxicity can be a result of Modeficiency and vice versa (McDowell, 2003; NAS/NRC, 1994a, 1980).

It is possible that receptor binding models (e.g., FIAM) 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, to predict metal toxicity using a mechanistic receptor binding approach in an Effects Addition model. Alternatively, if two metals do not compete for the same binding site on the organism, then these models 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. Additionally, this possibility, while improving the ability to assess the effects of metal mixtures, does not include temporal aspects (i.e., "time-to-response" versus concentration).

From the preceding discussion, it should be clear that the accurate prediction of joint toxicity of metal mixtures to terrestrial organisms remains a significant challenge.

6.3.4. Critical Body Residues

Critical body residues (CBRs) are internal concentrations of chemicals that are correlated with the onset of a toxic response (Conder et al., 2002; Lanno et al., 1998). CBRs can be based

on whole-body residues (see below for discussion of this approach in soil invertebrates) or concentrations in specific tissues. The risk assessor may choose to use CBRs instead of dietary TRVs to reduce uncertainties because they account for site-specific bioavailability and multipathway issues (Van Straalen, 1996; Van Wensem et al., 1994). Unfortunately, there are major data gaps in available CBRs for many species—metal combinations.

Risk assessors can use tissue-specific critical loads for some metals that have been established for several species of vertebrate wildlife, including Pb in liver, Cd in kidney, Hg in brains, and Se in eggs. See Beyer et al. (1996) for these figures. Only a few CBRs have been developed in soil invertebrates for metals (Conder et al., 2002; Crommentuijn et al., 1997, 1994; and Smit, 1997 for Cd and Zn).

For plants, the use of a tissue residue (CBR) approach is another method that risk assessors might use to address metal toxicity issues, based on the concept that a metal concentration must reach a threshold value in the organism or at the target site before effects begin to occur (McCarty and Mackay, 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 and there is little to no information available. Therefore, this approach, although conceptually sound, requires significant research before risk assessors will find it useful.

6.3.5. Plant and Soil Invertebrate Toxicity

The risk assessor can estimate TRVs (i.e., toxic thresholds) for plants and soil invertebrates from laboratory tests where metals are mixed with standard soils (Fairbrother et al., 2002). Variability among soil toxicity test results is due in part to the influence of soil properties on bioavailability of metals (e.g., pH, organic matter and CEC). Additionally, acclimation and adaptation of test organisms can further complicate test results and aging and other physical/chemical processes that affect metal speciation and uptake are not represented. Because incorporation of sparingly soluble substances, such as many environmental forms of metals, into the soil matrix is difficult, tests generally are conducted using soluble metal salts with the addition of organism to the test matrix immediately after mixing. The risk assessor should be aware of how all these factors influence the test outcome and subsequent TRV derivation.

There is a large body of literature on toxicity of metals to soil organisms (e.g., van Straalen and Løkke, 1997), although often the objectives were to understand processes rather than to develop defensible toxicity thresholds. The challenge for the risk assessor, therefore, lies in how to use these data, taking into account the test-to-test variability in soil chemistry parameters, and how to 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. One approach to addressing variability in soil

toxicity tests is to normalize test results by dividing the LC₅₀ (or, more generally, the EC_x) by percent organic matter (Lock and Janssen, 2001). This approach is based on observed correlations between the LC₅₀ of Cu to earthworms and soil organic matter content (Lock and Janssen, 2001). More recently, CEC has been shown to be the most important factor modifying Zn bioavailability in soils for both invertebrates and plants. Because CEC is a function, at least in part, of soil pH, normalization using this parameter should be done only among soils of similar pH ranges. However, comparison of field data with laboratory toxicity response information still is best accomplished by measuring metals in soil pore water from field assessments and comparing such data to spiked laboratory soils. Risk assessors can use the guidance document developed for establishing Ecological Soil Screening Levels or Eco SSL to judge the applicability of literature studies to plant or soil invertebrate toxicity threshold determinations. Eco SSLs have been developed for several metals, and the risk assessor should refer to these for national or regional assessments and for screening level, site-specific assessments.

6.3.6. 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 Se (Adams et al., 2003), exposure of waterfowl to Pb-contaminated sediments (Henny et al., 2000; Beyer et al., 1998; Blus et al., 1991), and white-tailed ptarmigan exposure to Cd in vegetation (Larison et al., 2000). Most metals express multiorgan toxicity, resulting in a 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, mice, or domestic livestock species (e.g., cattle and chickens) exposed to soluble metal salts. Risk assessors will need to extrapolate the results of such tests to species of interest because of the paucity of data on the toxicity of metals to wildlife. However, risk assessors should approach this carefully 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 are the selected wildlife species. Toxicological responses vary among species because of many physiological factors that influence the toxicokinetics (absorption, distribution, and elimination) and toxicodynamics (relative potency) of metals after exposure has occurred. For example, differences in digestive tract physiology, renal excretion rates, and egg production influence the toxicokinetics of metals. The ability of some species to more rapidly produce protective proteins such as metallothionein after exposure to metals is a toxicodynamic features leading to interspecific extrapolation uncertainty. Thus, risk assessors should not extrapolate data from mammal studies to birds, and should be aware that 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, which some species are able to regulate or store 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. These difficulties in interspecific extrapolations are not unique to metals risk assessment except when dealing with essential elements. A review of potential extrapolation methodologies can be found in Kapustka et al. (2004).

Risk Characterization

Have the qualitative assessment, quantitative assessment, and key uncertainties regarding metals been presented in accordance with EPA guidelines?

Do conclusions fully reflect risks in relation to ambient concentrations, essentiality of metals, chemical speciation, and information on variability in species sensitivity?

Have assumptions and uncertainties been documented adequately?

Have available data on mechanisms of action and metal interactions been fully explored in developing the quantitative assessment in accordance with EPA Guidance on Mixtures Risk Assessment?

Currently, the best sources of information for the risk assessor on wildlife metal toxicity thresholds are NAS/NRC (1994a, 1980), McDowell (2003), and the documentation supporting development of Eco SSLs values. The Eco SSL document also includes an approach for screening studies for acceptability for use in derivation of toxicity thresholds for risk assessments, which can then be used for deriving site-specific TRVs for the most applicable endpoints. Risk assessors should apply uncertainty factors for extrapolation of data to species in a different taxonomic category (e.g., genus, family or class) with caution and include a discussion of uncertainty in the risk characterization. Summaries for some metals are available in Beyer et al. (1996) and Fairbrother et al. (1996).

6.4. RISK CHARACTERIZATION

Risk Characterization is the final phase of the risk assessment process, in which information from hazard characterization; dose-response assessment and exposure assessment are jointly considered to determine the actual likelihood of risk to exposed populations (U.S. EPA, 2000c, 1998a). The characterization also should discuss the uncertainties in the exposure and effects assessments, and the level of confidence in the overall determination of risk. At the same time, Risk Characterization is the first phase in the risk management process, in which information from the characterization is integrated into the consequences of rule-making or risk management, such as consideration of cost, alternative solutions, political considerations, community interactions.

Each Risk Characterization should include three components: a qualitative summary of each section of the risk assessment, a numerical risk estimate, and a description of assumptions and uncertainties. These descriptions of variability and uncertainty are particularly important for metals risk assessments given all the components and challenges discussed in this Framework document. These are in addition to the variability and uncertainties that are inherent in all risk

assessments (e.g., species to species toxicity extrapolations). Because information, knowledge, and tools are lacking for many of the metal-specific uncertainties, risk assessors should be particularly diligent in documenting whether these may result in an over- or under-estimation of risk (i.e., result in a conservative risk estimate or not). It is likely that site-specific risk assessments will have fewer uncertainties than regional or national scale assessments because risk assessors have access to local data on key issues such as specific metal species, relative bioavailability, or background metal levels. For national or regional assessments, selection of ranges or specific numbers for these values will depend upon the degree of conservatism desired by the risk assessor and, therefore, should be clearly documented during the Risk Characterization phase.

REFERENCES

- Abernathy, CO; Cantilli, R; Du, JT.; Levander, OA (1993) Essentiality versus toxicity; some considerations in the risk assessment of essential trace elements. In: Saxena, J, ed. Hazard assessment of chemicals. Washington, DC: Taylor and Francis; pp. 81B113.
- Adams, WJ; Brix, KV; Edwards, M; Tear, LM; DeForest, DK; Fairbrother, A. (2003) Analysis of field and laboratory data to derive selenium toxicity thresholds for birds. *Environ Toxicol Chem* 22(9):2020B2029.
- AIHA (American Industrial Hygiene Association). (2003) The occupational environment: its evaluation, control, and management. 2nd Edition. Dinardi, S, ed. Fairfax, VA: AIHA Press; pp. 37B38.
- Allen, HE. (2002) Bioavailability of metals in terrestrial ecosystems: importance of partitioning for bioavailability to invertebrates, microbes and plants. ISBN 1-880611-46-5. Pensacola, FL: SETAC Press, 158 pp.
- Allison, JD; Brown, DS; Novo-Gradac, KJ. (1991) MINTEQA2/PRODEFA2, a geochemical assessment model for environmental systems: version 3.0, user's manual. U.S.EPA ERL ORD, Athens, GA. EPA/600/3-91/021.
- Andersen, ME; Clewell, HJ; Gargas, ML; Smith, FA; Reitz, RH. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87(2):185B205.
- Ankley, GT; Phipps, GL; Leonard, EN; Benoit, DA; Mattson, VR. (1991) Acid-volatile sulfide as a factor mediating cadmium and nickel bioavailability in contaminated sediments. *Environ Toxicol Chem* 10:1299B1307.
- Ankley, GT; Di Toro, DM; Hansen, DJ; Berry, WJ. (1996) Technical basis and proposal for deriving sediment quality criteria for metals. *Environ Toxicol Chem* 15(12):2056B2066.
- ANZECC and ARMCANZ (Australian and New Zealand Environment and Conservation Council and Agriculture and Resource Management Council of Australia and New Zealand). (2000) Australian and New Zealand guidelines for fresh and marine water quality, Vols. 1 and 2. Available online at <http://www.deh.gov.au/water/quality/nwqms/index.html#monitor>
- Arnold, PT; Kapustka, LA. (1993) Comparative uptake kinetics and transport of cadmium and phosphate in *Phleum pratense*-*Glomus deserticum* associations. *Environ Toxicol Chem* 12:177B186.
- ATSDR (Agency for Toxic Substance and Disease Registry), (2003) Toxicological profile for nickel, draft for public comment. U.S. Public Health Service, U.S. Department of Human Services, (2003). Atlanta, GA.
- ATSDR (Agency for Toxic Substance and Disease Registry), Draft (2004) Evaluation of the toxicology of chemical mixtures commonly found at hazardous waste sites. U.S. Public Health Service, U.S. Department of Human Services, (2004). Atlanta, GA.
- AWWA (American Water Works Association). (1999) Water quality and treatment. A handbook of community water supplies. 5th ed. 1233 pp. ISBN 0-07-001659-3. New York, NY.
- Baas-Becking, LGM; Kaplan, IR; Moore, D. (1960) Limits of the natural environment in terms of pH and oxidation-reduction potentials. *J Geol* 68:243B284.
- Babukutty, Y; Chacko, J. (1995) Chemical partitioning and bioavailability of lead and nickel in an estuarine system. *Environ Toxicol Chem* 14:427B434.
- Bailey, RG. (1983) Delineation of ecosystem regions. *Environ. Management* 7(4): 365-373.

Bailey, RG; Avers, PE; King, T; McNab, WH, eds. (1994) Ecoregions and subregions of the United States (map) US Geological Survey. Scale 1:7,500,000. Washington, DC: USDA Forest Service. With supplementary table of map unit descriptions, compiled and edited by W. H. McNab and R. G. Bailey. Available online at <http://www.fs.fed.us/land/pubs/ecoregions/toc.html>

Baines, SB; Fisher, NS; Stewart, R. (2002) Assimilation and retention of selenium and other trace elements from crustacean food by juvenile striped bass (*Morone saxatilis*). *Limnol Oceanogr* 47(3):646-655.

Ballatori, N. (2002) Transport of toxic metals by molecular mimicry. *Environ Health Perspect* 110(Suppl 5):689B694.

Barak, P. (1999) Essential elements for plant growth. Department of Soil Science, University of Wisconsin-Madison. Available online at <http://www.soils.wisc.edu/~barak/soilscience326/essentl.htm>.

Barber, SA. (1995) Soil nutrient bioavailability: a mechanistic approach, 2nd ed. New York, NY: John Wiley & Sons.

Barnes, RM. (1990) Childhood soil ingestion: how much dirt do kids eat? *Anal Chem* 62(19):1023B1033.

Barnhart, J. (1997) Chromium chemistry and implications for environmental fate and toxicity. *J Soil Contam* 6(6):561-568.

Basta, NT; Pantone, DJ; Tabatabai, MA. (1993) Path analysis of heavy metal adsorption by soil. *Agron J* 85:1054B1057.

Beck, BD; Mattuck, RL; Bowers, TS; Cohen, JT; O'Flaherty, E. (2001) The development of a stochastic physiologically-based pharmacokinetic model for lead. *Sci Total Environ* 274(1-3):15B19.

Bell, PF; Adamu, CA; Mulchi, CL; McIntosh, M; Chaney, RL. (1988) Residual effects of land applied municipal sludge on tobacco. I. Effects on heavy metals concentrations in soils and plants. *Tob Sci* 32:33B38.

Berglund, M; Askesson, A; Nermell, B; Vahter, M. (1994) Intestinal absorption of dietary cadmium in women depends on body stores and fiber intake. *Environ Health Perspect* 102(12):1058B1065.

Berry, WJ; Hansen, DJ; Mahony, JD; D.L. Robson, DL; DiToro, DM; Shipley, BP; Rogers, B; Corbin, JM and W.S. Boothman, WS. (1996) Predicting the toxicity of metal-spiked laboratory sediments using acid-volatile sulfide and interstitial water normalizations. *Environ Toxicol Chem* 15(12):2067B2079.

Beyer, WN; Heinz, GH; Redmon-Norwood, AW. (1996) Environmental contaminants in wildlife: interpreting tissue concentrations. Boca Raton, FL: Lewis Publishers.

Beyer, WN; Audet, DJ; Morton, A; Campbell, JK; LeCaptain, L. (1998) Lead exposure of waterfowl ingesting Coeur d'Alene River Basin sediments. *J Environ Qual* 27(6):1533B1538.

Bingham, FT; Sposito, G; Strong, JE. (1986) The effect of sulfate on the availability of cadmium. *Soil Sci* 141(2):172B177.

Bjerregaard, P; Topçuoğlu, S; Fisher, NS; Fowler, SW. (1985) Accumulation and retention of ²³⁷Pu and ²⁴¹Am in the mussel *Mytilus edulis*. *Mar Ecol Prog Ser* 21:99B111.

Blus, LJ; Henny, CJ; Hoffman, DJ; Grove, RA. (1991) Lead toxicosis in tundra swans near a mining and smelting complex in northern Idaho. *Arch Environ Contam Toxic* 21:549B555.

Bodek, IB; Lyman, WJ; Reehl, WF; Rosenblatt, DH, eds. (1988) Environmental inorganic chemistry: properties, processes, and estimation methods. SETAC Spec. Publ. Ser. New York, NY: Pergamon Press.

- Bohn, HL; McNeal, BL; O'Connor, GA. (1985) Soil chemistry, 2nd ed. New York, NY: John Wiley & Sons.
- Bolger, PM; Yess, NJ; Gunderson, EL; Troxell TC; Carrington CD. (1996) Identification and reduction of sources of dietary lead in the United States. *Food Additives Contam* 13:53B60.
- Borgmann, U; Norwood, WP; Dixon, DG. (2004) Re-evaluation of metal bioaccumulation and chronic toxicity in *Hyalella azteca* using saturation curves and the biotic ligand model. *Environ Pollut* 131(3):469-484.
- Bose, A; Vashistha, K; O'Loughlin, BJ: (1983) Azarcón por empacho - another cause of lead toxicity. *Pediatrics* 72(1): 106-108.
- Bowers, TS; Beck, BD; Karam, HS. (1994) Assessing the relationship between environmental lead concentrations and adult blood lead levels. *Risk Anal* 14(2):183B189.
- Bradham, KD. (2002) Effect of soil properties on the bioavailability and toxicity of metals to *Eisenia andrei*. Ph.D. dissertation. Dept. of Zoology, Oklahoma State University.
- Brown, DS; Allison, JD. (1987) MINTEQA1, an Equilibrium Metal Speciation Model. User's Manual. U.S. Environmental Protection Agency, Athens, GA. EPA-600-3-87-012.
- Brown, GE, Jr; Foster, AL; Ostergren, JD. (1999) Mineral surfaces and bioavailability of heavy metals: a molecular-scale perspective. *Proc Natl Acad Sci* 96(7):3388B3395.
- Brown, SL; Henry, CL; Compton, H; Chaney, RL, Pannella, D. (2000) Using municipal biosolids in combination with other residuals to restore metal-contaminated mining areas. In: Proceedings of a symposium on mining, forest and land restoration: the successful use of residual/biosolids/organic matter for reclamation activities. Rocky Mountain Water Environment Association. July 17B20, Denver, CO.
- Brumbaugh, WG; Ingersoll, CG; Kemble, NE; May, TW; Zajicek, JL. (1994) Chemical characterization of sediments and pore water from the Upper Clark Fork River and Milltown Reservoir, Montana. *Environ Sci Chem* 13:1971B1983.
- Bullock, OR. (2000a) Current methods and research strategies for modeling atmospheric mercury. *Fuel Proc Technol* 65B66:459B471.
- Bullock, OR. (2000b) The importance of emissions speciation to the atmospheric transport and deposition of mercury. Presented at: EPA Conference on Assessing and Managing Mercury From Historic and Current Mining Activities, San Francisco, CA, November 28 30.
- Bullock, OR; Brehme, KA. (2002) Atmospheric mercury simulation using the CMAQ model: formulation description and analysis of wet deposition results. *Atmos Environ* 36(13):2135B2146.
- Butcher, J; Diamond, J; Berr, J; Latimer, H; Klaine, T; Hoang, T; Bowersox, M. (2006) Toxicity models of pulsed copper exposure to *Pimephales promelas* and *Daphnia magna*. *Environ Toxicol Chem* 25(9):2541-2550.
- Calabrese, EJ; Stanek, EJ; Gilbert, CE; Barnes, RM. (1990) Preliminary adult soil ingestion estimates: results of a pilot study. *Regul Toxicol Pharmacol* 12(1):88B95.
- Calamari, D; Alabaster, JS. (1980) An approach to theoretical models in evaluating the effects of mixtures of toxicants in the aquatic environment. *Chemosphere* 9(9):533B538.
- Campbell, PGC. (1995) Interactions between trace metals and aquatic organisms: a critique of the free ion activity model. In: Tessier, A; Turner, DR, eds. *Metal speciation and bioavailability in aquatic systems*. Chichester, UK: Wiley; pp. 45B102.
- Campbell, PGC; Hansen, HJ; Dubreuil, B; Nelson, WO. (1992) Geochemistry of Quebec North Shore salmon rivers during snowmelt: organic acid pulse and aluminum mobilization. *Can J Fish Aquat Sci* 49:1938B1952.

Capar, SG; Cunningham, WC. (2000) Element and radionuclide concentrations in food: FDA total diet study 1991-1996. *J AOAC Internat* 83(1):157B177.

Carignan, R; Tessier, A. (1985) Zinc deposition in acid lakes: the role of diffusion. *Science* 228(4707):1524B1526.

Carlisle, J; Christopher, J; Davis, B; Klein, K; Renzi, B; Wade, M. (2000) Updated version of the California EPA lead risk assessment spreadsheet model for predicting blood lead in children and adults. Society of Toxicology, March. Available online at http://www.dtsc.ca.gov/AssessingRisk/HERD_Research_Presentations.cfm.

Carlisle, JC; Wade, MJ. (1992) Predicting blood lead concentrations from environmental concentrations. *Regul Toxicol Pharmacol* 16(3):280B289.

Carlson, AR; Phipps, GL; Mattson, VR (1991) The role of acid-volatile sulfide in determining cadmium bioavailability and toxicity in freshwater sediments. *Environ Toxicol Chem* 10:1309B1319.

Casas, AM; Crecelius, EA. (1994) Relationship between acid volatile sulfide and the toxicity of zinc, lead and copper in marine-sediments. *Environ Toxicol Chem* 13:529B536.

CDC (Centers for Disease Control and Prevention). (1981) Use of lead tetroxide as a folk remedy for gastrointestinal illness. *Morbidity and Mortality Weekly Report* 30(43):546-547.

CDC (Centers for Disease Control and Prevention). (1982) Lead poisoning from lead tetroxide used as a folk remedy--Colorado. *Morbidity and Mortality Weekly Report* 30(52):647-648.

CDC (Centers for Disease Control and Prevention). (1983) Folk remedy-associated lead poisoning in Hmong children--Minnesota. *Morbidity and Mortality Weekly Report* 32:555-556. Available online at <http://www.cdc.gov/mmwr/preview/mmwrhtml/00000165.htm>.

CDC (Centers for Disease Control and Prevention). (2003) Second national report on human exposure to environmental chemicals. January. NCEH Pub No. 03-0022.

CDC (Centers for Disease Control and Prevention). (2005). Third National report on human exposure to environmental chemicals. July. NCEH Pub. No. 05-0570. Available online at <http://www.cdc.gov/exposurereport/3rd/pdf/thirdreport.pdf>.

Chaney, RL. (1980) Health risks associated with toxic metals in municipal sludge. In; Bitton, G; Damron, BL; Edds, GT; Davidson, JM; eds. *Sludge--Health risks of land application*. Ann Arbor, MI: Ann Arbor Science Publishers, Inc.; pp. 59B83.

Chaney, RL; Ryan, JA. (1993) Heavy metals and toxic organic pollutants in MSW-composts: Research results on phytoavailability, bioavailability, etc. In: Hoitink, AJ; Keener, HM, eds. *Science and engineering of composting: Design, environmental, microbiological and utilization aspects*. Columbus, OH: Ohio State University; pp. 451B506.

Chaney, RL; Ryan, JA. (1994) Risk based standards for arsenic, lead and cadmium in urban soils. Frankfurt, Germany: DECHMEA.

Chaney, RL; Brown, SL; Angle, JS; Stuczynski, TI; Daniels, WL; Henry, CL; Siebielec, G; Li, YM; Malik, M; Ryan JA and Compton H. (2000) In situ remediation/reclamation/restoration of metals contaminated soils using tailor made biosolids mixtures. In: *Proceedings of Mining, Forest and Land Restoration Symposium/Workshop*. Rocky Mountain Water Environment Association Biosolids Committee, July 17 19, Golden, CO.

Chang, SI; Reinfelder, JR. (2000) Bioaccumulation, subcellular distribution and trophic transfer of copper in a coastal marine diatom. *Environ Sci Technol* 34(23):4931-4935.

Chapman, PM; Wang, F. 1998. Issues in ecological risk assessments of inorganic metals and metalloids. Available online at <http://www.uoguelph.ca/cntc/files/era-metals.pdf>. HERAC(6):965-988.

- Chen, Z; Mayer, LM. (1998) Mechanisms of Cu solubilization during deposit feeding. *Environ Sci Technol* 32(6):770–775.
- Chen, Z; Mayer, LM. (1999) Sedimentary metal bioavailability determined by the digestive constraints of marine deposit feeders: Gut retention time and dissolved amino acids. *Mar Ecol Prog Ser* 176: 139–151.
- Choudhury, H; Harvey, T; Thayer, WC; Lockwood, TF; Stiteler WM; Goodrum, PE; Hassett, JM; Diamond, GL (2001) Urinary cadmium elimination as a biomarker of exposure for evaluating a cadmium dietary exposure-biokinetics model. *J Toxicol Environ Health* 63:101B130.
- Clarke, RH. (1995) ICRP recommendations applicable to the mining and minerals processing industries and to natural sources. International Commission on Radiological Protection. *Health Phys* 69:454B460.
- Clarkson, TW. (1993) Molecular and ionic mimicry of toxic metals. *Ann Rev Pharmacol Toxicol* 32:545B571.
- Clason, B; Langston, WJ; Zauke, GP. (2004) Bioaccumulation of trace metals in the amphipod *Chaetogammarus marinus* (Leach, 1815) from the Avon and Tamar estuaries (UK): comparison of two-compartment and hyperbolic toxicokinetic models. *Marine Environ Res* 57(3):171-195.
- Clayton, CA; Pellizzari, ED; Whitmore, R; Perritt, RL. and Quackenboss, JJ. (1999) National human exposure assessment survey (NHEXAS): distributions and associations of lead, arsenic and volatile organic compounds in EPA Region 5. *J Exp Anal Environ Epidemiol* 9(5):381B392.
- Clayton, CA; Pellizzari, ED; Quackenboss, JJ. (2002) National Human Exposure Assessment Survey: analysis of exposure and routes for arsenic and lead in EPA Region 5. *J Exp Anal Environ Epidemiol* 12(1):29B43.
- Cohen, JT; Beck, BD; Bowers, TS; Bornschein, RL; Calabrese, EJ. (1998) An arsenic exposure model: Probabilistic validation using empirical data. *Hum Ecol Risk Assess* 4(2):341B377.
- Cohen, SM; Klaunig, J.; Meek, ME; Hill, RN; Pastoor, T; Lehman-McKeeman, L.; Bucher, J; Longfellow, DG; Seed, J; Dellarco, V; Fenner-Crisp, P; Dorothy, P. (2004) Evaluating the human relevance of chemically induced animal tumors. *Toxicol Sci* 78(2):181–186.
- Conder, JM; Seals, LD; Lanno, RP. (2002) Method for determining toxicologically relevant cadmium residues in the earthworm *Eisenia fetida*. *Chemosphere* 49:1B7.
- Cook, PM; Carlson, AR; Lee, H. (1989) Tissue residue approach. In: *Sediment classification methods compendium*, Chapter 7. U.S. EPA Office of Water, Washington, DC; EPA 823-R-92-006.
- Cook, PM; Erickson, RJ; Spehar, RL; Bradbury, SP; Ankley, GT. (1993) Interim report on data and methods for assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin risks to aquatic life and associated wildlife. U.S. EPA, Office of Research and Development, Duluth, MN; EPA/600/R-93/055.
- Crecelius, EA; Hardy, JT; Gibson, CI; Schmidt, RL; Apts CW; Gurtisen, JM and Joyce, SP. (1982) Copper bioavailability to marine bivalves and shrimp: Relationship to cupric ion activity. *Mar Environ Res* 6:13B26.
- Crommentuijn, T; Doodeman, CJAM; Doornekamp, A; Van der Pol, JJC; Bedaux, JJM; van Gestel, CAM (1994) Lethal body concentrations and accumulation patterns determine time-dependent toxicity of cadmium in soil arthropods. *Environ Toxicol Chem* 13(17):1781B1789.
- Crommentuijn, T; Doodeman, CJAM; Van der Pol, JJC; Doornekamp, A; Rademaker, MCJ; van Gestel, CAM (1997) Bioavailability and ecological effects of cadmium on *Folsomia candida* (Willem) in an artificial soil substrate as influenced by pH and organic matter. *Appl Soil Ecol* 5:261B271.
- Dabeka, RW; McKenzie, AD. (1995) Survey of lead, cadmium, fluoride, nickel, and cobalt in food composites and estimation of the dietary intakes of these elements by Canadian adults and children. *J AOAC Internat* 78(4):897B909.

Dabeka, RW; McKenzie, AD; Lacroix, GM; Cleroux, C; Bowe, S; Graham, RA; Conacher, HB; Verdier P. (1993) Survey of arsenic in total diet food composites and estimation of the dietary intake of arsenic by Canadian adults and children. *J AOAC Internat* 76(1):14B25.

Dang, W; Chen, J; Mottl, N; Phillips, L; Wood, P; McCarthy, S; Lee, R; Helmke, M; Nelson, M; Coon, K. (2003) A probabilistic risk assessment for children who contact CCA-treated playsets and decks. Available online at <http://www.epa.gov/scipoly/sap/meetings/2003/december3/shedsprobabalisticriskassessmentnov03.pdf>.

Degryse, F; Buekers, J; Smolders, E. (2004) Radio-labile cadmium and zinc in soils as affected by pH and source of contamination. *European Journal of Soil Science* 55(1): 113-122.

Delos, CG; Richardson, WL; DePinto, JV; Ambrose, RB; Rodgers, W; Rygwelski, K; St. John, J; Shaughnessy, WJ; Faha, TA. (1984) Technical guidance manual for performing waste load allocations: Book II, streams and rivers. Chapter 3: Toxic Substances. U.S. Environmental Protection Agency, Office of Water, Washington, DC; EPA/440/9-84-022.

DeMoor, JM; Koropatnick, DJ. (2000) Metals and cellular signaling in mammalian cells. *Cell Mol Biol* 46(2):367-81.

De Schamphelaere, KAC; Janssen, CR. (2002) A biotic ligand model predicting acute copper toxicity for *Daphnia magna*: The effects of calcium, magnesium, sodium, potassium and pH. *Environ Sci Technol* 36(1):48B54.

De Schamphelaere, KAC; Janssen, CR. (2004) Development and field validation of a biotic ligand model predicting chronic copper toxicity to *Daphnia magna*. *Environ Toxicol Chem* 23(6):1365B1375.

De Schamphelaere, KAC; Heijerick, DG; Janssen, CR. (2002) Refinement and field validation of a biotic ligand model predicting acute copper toxicity to *Daphnia magna*. Special issue: the biotic ligand model for metals. Current research, future directions, regulatory implications. *Comp Biochem Physiol C* 133(1-2):243B258.

De Schamphelaere, KAC; Vasconcelos, FM; Heijerick, DG; Tack, FMG; Delbeke, K; Allen, HE; Janssen, CR. (2003) Development and field validation of a predictive copper toxicity model for the green alga *Pseudokirchneriella subcapitata*. *Environ Toxicol Chem* 22(10): 2454-2465.

De Schamphelaere, KAC; Vasconcelos, FM; Tack, FMG; Allen, HE; Janssen, CR. (2004) Effect of dissolved organic matter source on acute copper toxicity to *Daphnia magna*. *Environ Toxicol Chem* 23(5):1248-1255.

Diamond, ML. (1995) Application of a mass balance model to assess in-place arsenic pollution. *Environ Sci Technol* 29(1):29-42.

Diamond ML; Mudroch A. (1990) Review of techniques for quantifying the transfer of contaminants and nutrients from bottom sediments. National Water Research Institute Contribution No. 90-43, National Water Research Institute, Environment Canada, Burlington, Ontario, Canada.

Di Toro, DM; Mahony, JD; Hansen, DJ; Scott, KJ; Hicks, MB; Mayr, SM; Redmond, MS. (1990) Toxicity of cadmium in sediments: the role of acid volatile sulfide. *Environ Toxicol Chem* 9:1487B1502.

Di Toro, DM; Mahony, JD; Hansen, DJ; Scott, KJ; Carlson, AR; Ankley, GT. (1992) Acid volatile sulfide predicts the acute toxicity of cadmium and nickel in sediments. *Environ Sci Tech* 26(1):96-101.

Di Toro, DM, Allen, HE; Bergman, HL; Meyer, JS; Paquon, PR; Santore, RC. (2001) Biotic ligand model of the acute toxicity of metals. I. technical basis. *Environ Tox Chem* 20(10):2383B2396.

Dzombak, DA; Ali, MA. (1993) Hydrochemical modeling of metal fate and transport in freshwater environments. *Water Pollut Res J Can* 28(1):7B50.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). (2001) Aquatic toxicity of mixtures. Technical Report No. 80. Brussels, Belgium; 63 pp.

- Efroymsen, RA; Sample, BE; Suter GW, II. (2004) Bioaccumulation of inorganic chemicals from soil by plants: Spiked soils vs. field contamination on background. *Hum Ecol Risk Assess* 10(6) 1117-1127.
- Egan, SK; Tao, SS; Pennington, JA; Bolger, PM. (2002) U.S. Food and Drug Administration's total diet study: intake of nutritional and toxic elements, 1991-1996. *Food Addit Contam* 19(2):103-125.
- Ellis, KJ; Vartsky, D; Zanzi, I; Cohn, SH; Yasumura, S. (1979) Cadmium: in vivo measurement in smokers and nonsmokers. *Science* 205:323B325.
- Enserink, EL; Maas-Diepeveen, JL; Van Leeuwen, CJ. (1991) Combined effects of metals: an ecotoxicological evaluation. *Water Res* 25(6):679B687.
- Erickson, RJ; Benoit, DA; Mattson, VR; Nelson, HP Jr.; Leonard, EN. (1996) The effects of water chemistry on the toxicity of copper to fathead minnows. *Environ Toxicol Chem* 15(2): 181-193.
- Escher, BI; Hermens, JLM. (2002) Modes of action in ecotoxicology: their role in body burdens, species sensitivity, QSARs, and mixture effects. *Environ Sci Technol* 36(2):4201-4217.
- Fairbrother, A; Kapustka, LA. (1997) Hazard classification of inorganic substances in terrestrial systems: a discussion paper. Ottawa, Canada: International Council on Metals and the Environment.
- Fairbrother, A; Locke, L; Hoff, GL, eds. (1996) Non-infectious diseases of wildlife. 2nd ed. Ames, IA: Iowa State University Press.
- Fairbrother, A; Glazebrook, PW; van Straalen, NM; Tarazona, JV, eds. (2002) Test methods for hazard determination of metals and sparingly soluble metal compounds in soils. Pensacola, FL: SETAC Press.
- Fan, W; Wang, W-X. (2001) Sediment geochemical controls on Cd, Cr, and Zn assimilation by the clam *Ruditapes philippinarum*. *Environ Toxicol Chem* 20(10):2309B2317.
- Fargašová, A. (2001) Winter third- to fourth-instar larvae of *Chironomus plumosus* as bioassay tools for assessment of acute toxicity of metals and their binary combinations. *Ecotoxicol Environ Saf* 48(1):1B5.
- Finney, DJ. (1947) Probit analysis: a statistical treatment of the sigmoidal response curve. Cambridge, UK: Cambridge University Press.
- Fisher, NS; Reinfelder, JR. (1995) The trophic transfer of metals in marine systems. In: Tessier, A; Turner, DR, eds. *Metal speciation and bioavailability in aquatic systems*. Chichester, UK: Wiley; pp. 363-406.
- Fisher, NS; Teyssié, J-L; Fowler, SW; Wang, W-X. (1996) Accumulation and retention of metals in mussels from food and water: a comparison under field and laboratory conditions. *Environ Sci Technol* 30(11):3232B3242.
- Fisher, NS; Stupakoff, I; Sañudo-Wilhelmy, SA; Wang, W-X; Teyssié, J-L; Fowler, SW; Crusius, J. (2000) Trace metals in marine copepods: a field test of a bioaccumulation model coupled to laboratory uptake kinetics data. *Mar Ecol Prog Ser* 194:211-218.
- Forstner, U. (1995) Non-linear release of metals from aquatic sediments. In: Salomons, W; Stigliani, WM, eds. *Biogeochemistry of pollutants in soils and sediments*. Germany: Springer-Verlag.
- Freeman, GB; Johnson, JD; Killinger, JM; Liao, SC; Davis, AO; Ruby, MV; Chaney, RL; Lovre, SC; Bergstrom, PD. (1993) Bioavailability of arsenic in soil impacted by smelter activities following oral administration in rabbits. *Fundam Appl Toxicol* 21(1):83B88.
- Freeman, GB; Schoof, RA; Ruby, MV; Davis, AO; Dill, JA; Liao, SC; Lapin, CA; Bergstrom, PD. (1995) Bioavailability of arsenic in soil and house dust impacted by smelter activities following oral administration in cynomolgus monkeys. *Fundam Appl Toxicol* 28(2):215B222.
- Friis, L; Petersson, L; Edling, C. (1998) Reduced cadmium levels in human kidney cortex in Sweden. *Environ Health Perspect* 106(4):175B178.

- Gagnon, C; Fisher, NS. (1997) The bioavailability of sediment-bound Cd, Co, and Ag to the mussel *Mytilus edulis*. *Can J Fish Aq Sci* 54:147-156.
- Geffner, ME; Sandler, A. (1980) Oral metallic mercury: a folk remedy for gastroenteritis. *Clinical Pediatrics* 19(6): 435–437.
- George, E; Römheld, V; Marschner, H. (1994) Contribution of Mycorrhizal fungi to micronutrient uptake by plants. In: Manthey, JA; D.E. Crowley, DE; Luster, DG; eds. *Biochemistry of metal micronutrients in the rhizosphere*. Boca Raton, FL: Lewis Publishers; pp. 93B110.
- Gobas, FAPC: (1993) A model for predicting the bioaccumulation of hydrophobic organic chemicals in aquatic food webs: application to Lake Ontario. *Ecol Modell* 69(1-2):1-17.
- Goyer, R; Golub, M; Choudhury, H; Hughes, M; Kenyon, E; Stifelman, M. (2004) Issue paper on the human health effects of metals. August 19, 2004. Available online at <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=59052>
- Graziano, JH; Blum, CB; LoIacono, NJ; Slavkovich, V; Manton, WI; Pond, S; Moore, MR. (1996) A human in vivo model for the determination of lead bioavailability using stable isotope dilution. *Environ Health Perspect* 104:176B179.
- Griffith, GE; Omernik, JM; Woods, AJ. (1999) Ecoregions, watersheds, basins, and HUCs: how state and federal agencies frame water quality. *Soil and Water Conserv* 54(4):666-677.
- Griscom, SB; Fisher, NS; Luoma, SN. (2002) Kinetic modeling of Ag, Cd and Co bioaccumulation in the clam *Macoma balthica*: quantifying dietary and dissolved sources. *Mar Ecol Prog Ser.* 240:127-141.
- Gunderson, BL. (1995) FDA total diet study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. *J AOAC Internat* 78(6):1353B1363.
- Guo, Z. (2002) Review of indoor emission source models. *Overview Environ Pollut* 120(3):533B549.
- Hamon, R; McLaughlin, MJ; Naidu, R; Correll, R. (1998) Long-term changes in cadmium bioavailability in soil. *Environ Sci Technol* 32(23):3699-3703.
- Handy, RD. (1993) The effect of acute exposure to dietary Cd and Cu on organ toxicant concentrations in rainbow trout, *Oncorhynchus mykiss*. *Aquat Toxicol* 27:1-14.
- Hanson, DJ; Berry, WJ; Mahony, JD; Boothman, WS; DiToro, DM; Robson, DL; Ankley, GT; Ma, D; Yan, Q; Pescht, CE. (1996) Predicting the toxicity of metal contaminated field sediments using interstitial concentrations of metals and acid volatile sulfide normalizations. *Environ Toxicol Chem* 15(12):2080B2094.
- Hare, L; Tessier, A; Borgmann, U. (2003) Metal sources for freshwater invertebrates: pertinence for risk assessment. *Human Ecol Risk Assess* 9:779B793.
- Hathcock, JN (1996) Safety limits for nutrients. *J Nutr* 126(9):2386S-2389S.
- Hawley, JK. (1985) Assessment of health risk from exposure to contaminated soil. *Risk Anal* 5(4):289B302.
- Haygarth, PM; Jones, KC. (1992) Atmospheric deposition of metals to agricultural surfaces. In: Adriano, DC, ed. *Biogeochemistry of trace metals*. Boca Raton, FL: CRC/Lewis Publishers; pp. 249B276.
- Heijerick, DG; de Schamphelaere; KAC; Janssen, CR. (2000) Predicting acute zinc toxicity for *Daphnia magna* as a function of key water chemistry characteristics: development and validation of a biotic ligand model. *Environ Toxicol Chem* 21(6):1309-1315.
- Heijerick, DG; De Schamphelaere, KAC; Janssen, CR. (2002) Biotic ligand model development predicting Zn toxicity to the alga *Pseudokirchneriella subcapitata*: possibilities and limitations. *Comp Biochem Physiol C* 133(1-3):207-218.

- Henderson, RF; Bechtold, WE; Bond, JA; Sun, JD. (1989) The use of biological markers in toxicology. *Crit Rev Toxicol* 20:65-82.
- Henny, CJ; Blus, LJ; Hoffman, DJ; Sileo ,L; Audet, DJ; Snyder, MR. (2000) Field evaluation of lead effects on Canada geese and mallards in the Coeur d'Alene River Basin, Idaho. *Arch Environ Contam Toxicol* 39(1):97B112.
- Herkovits, J; Pérez-Coll, CS; Herkovits, FD. (1999) Evaluation of nickel-zinc interactions by means of bioassays with amphibian embryos. *Ecotoxicol Environ Safe* 45(3):266-273.
- Hook, SE. (2001) Sublethal toxicity of metals to copepods. Ph.D. dissertation. State University of New York (SUNY) at Stony Brook.
- Hook SE; Fisher, NS. (2001a) Reproductive toxicity of metals in calanoid copepods. *Mar Biol* 138:1131-1140.
- Hook SE; Fisher, NS. (2001b) Sublethal effects of silver in zooplankton: importance of exposure pathways and implications for toxicity testing. *Environ Toxicol Chem* 20:568-74.
- Hook, SE; Fisher, NS. (2002) Relating the reproductive toxicity of five ingested metals in calanoid copepods with sulfur affinity. *Marine Environ Res* 53(2):161B174.
- Hostynek, JJ; Hinz, RS; Lorence, CR; Guy, RH. (1998) Human skin penetration by metal compounds. In: Roberts, MS; Walters, KA; eds. *Dermal absorption and toxicity assessment*. New York, NY: Marcel Dekker, Inc.
- Hudson, RJM; Gherini, SA; Watras, CJ; Porcella, DB. (1994) A mechanistic model for the biogeochemical cycle of mercury in lakes. In: Watras, CJ; Huckabee, JW; eds. *Mercury as a global pollutant*. Chelsea, MI: Lewis Publishers.
- Huheey, JE; Keiter EA; Keiter, RI. (1993) *Inorganic chemistry—principles of structure and reactivity*. 4th ed. New York: Harper Collins College Publishers, 964 pp.
- Hursh, JB; Clarkson, TW; Miles, EF; Goldsmith, LA. (1989) Percutaneous absorption of mercury vapor by man. *Arch Environ Health* 44(2):120B127.
- IARC (International Agency for Research on Cancer). (2004) Recent Meetings Volume 87: Inorganic and organic lead compounds 10–17 February 2004. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Available online at <http://monographs.iarc.fr/ENG/Meetings/vol87.php>
- IARC (International Agency for Research on Cancer). (2004b) Volume 84: Some drinking-water disinfectants and contaminants, including arsenic. Available online at <http://monographs.iarc.fr/ENG/Monographs/vol84/volume84.pdf> .
- Ilyin, LA; Ivannikov, AT; Parfenov, YD; Stolyarov, VP. (1975) Strontium absorption through damaged and undamaged human skin. *Health Phys* 29(1):75B80.
- IPCS (International Programme on Chemical Safety). (1990b) Beryllium. Environmental health criteria document No. 106. Geneva, Switzerland. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc106.htm>.
- IPCS (International Programme on Chemical Safety). (1994a) Environmental health criteria 170, assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc170.htm>.
- IPCS (International Programme on Chemical Safety). (1994b) Environmental health criteria 155, biomarkers and risk assessment: concepts and principles. United Nations Environment Programme, International Labour Organization, World Health Organization. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc155.htm>
- IPCS (International Programme on Chemical Safety). (1999) Environmental health criteria 210, principles for the assessment of risks to human health from exposure to chemicals. United Nations Environment Programme, International Labour Organization, World Health Organization.

IPCS (International Programme on Chemical Safety). (2000) Environmental health criteria 214, human exposure assessment. United Nations Environment Programme, International Labour Organization, World Health Organization. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc214.htm>.

IPCS (International Programme on Chemical Safety). (2001) Environmental health criteria 222, biomarkers in risk assessment: validity and validation. United Nations Environment Programme, International Labour Organization, World Health Organization. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc222.htm>.

IPCS (International Programme on Chemical Safety). (2002) Environmental health criteria 228, principles and methods for the assessment of risk from essential trace elements, United Nations Environment Programme, International Labour Organization, World Health Organization. Available online at <http://www.inchem.org/documents/ehc/ehc/ehc228.htm>.

Jaffe, D; Landis, MS; Weisspenzias, P; et al. (2003) Comments on “mercury concentrations in coastal California precipitation: Evidence of local and trans Pacific fluxes of mercury to North America,” by Steding and Flegal. *J Geophys Res Atmos* 108(D17): ACH 11 1BACH 11 2.

James, AC; Stahlhofen, W; Rudolf, GR; Köbrich, R; Briant, KS; Egan, MJ; Nixon, W; Birchall, A. (1994) Deposition of inhaled particles. *Annals of the ICRP* (Pub. No. 66) 24(1B3):231B299.

James, BR; Petura, JC; Vitale, RJ; Mussoline, GR. (1997) Oxidation-reduction chemistry of chromium: Relevance to the regulation and remediation of chromate-contaminated soils. *Soil Contam* 6(6):569-580.

Janssen, C; Muysen, B. (2001) Essentiality of metals: consequences for environmental risk assessments. Fact sheet #5 on environmental risk assessment. Ottawa, Ontario, Canada: International Council on Metals and the Environment.

Jarman, WM; Hobson, KA; Sydeman, WJ; Bacon, CE; McLaren, EB. (1996) Influence of trophic position and feeding location on contaminant levels in the Gulf of the Farallones food web revealed by stable isotope analysis. *Environ Sci Technol* 30(2):654-660.

Jing, J; Logan, T. (1992) Effects of sewage sludge cadmium concentration on chemical extractability and plant uptake. *J Environ Qual* 21:73B81.

Kabata-Pendias, A; Pendias, H. (2001) Trace elements in soil and plants. Boca Raton, FL: CRC Press; pp. 396.

Kahle, J; Zauke, G-P. (2003) Bioaccumulation of trace metals in the Antarctic amphipod *Orchomene plebs*: evaluation of toxicokinetic models. *Marine Environ Res* 55(5):359B384.

Kapustka, LA; Clements, WH; Ziccardi, L; Paquin, PR; Sprenger, M; Wall, D. (2004) Issue paper on the ecological effects of metals. Available online at <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>.

Kidd, KA; Hesslein, RH; Fudge, RP; Hallard, KA. (1995) The influence of trophic level as measured by delta-n-15 on mercury concentrations in fresh-water organisms. *Water Air and Soil Pollution* 80(1-4):1011-1015.

Kimber, I; Basketter, DA. (1996) Contact hypersensitivity to metals. In: Chang LW; Toxicology of metals. Boca Raton, FL: CRC Press; pp. 827-834.

Kiss, T; Osipenko, ON. (1994) Toxic effects of heavy metals on ionic channels. *Pharmacol Rev* 46(3):245-67.

Könemann, H. (1981) Quantitative structure-activity relationships in fish toxicity studies Part 1: relationship for 50 industrial pollutants. *Toxicology* 19(3):209-221.

Krishnan, K; Andersen, ME. (1994) Physiologically based pharmacokinetic modeling in toxicology In: Hayes, AW, ed. Principles and methods in toxicology, 3rd ed. New York, NY: Raven Press, Ltd.; pp. 149B188.

Landis, MS; Stevens, RK. (2003) Comments on “Measurements of atmospheric mercury species at a coastal site in the Antarctic and over the south Atlantic Ocean during polar summer.” *Environ Sci Technol* 37(14):3239B3240.

- Landrum, PF; Lee, H; Lydy, MJ. (1992) Toxicokinetics in aquatic systems: model comparisons and use in hazard assessment. *Environ Toxicol Chem* 11(12):1709-1725.
- Landrum, PF; Steevens, JA; Gossiaux, DC; McElroy, M; Robinson, S; Begnoche, L; Chernyak, S; Hickey, J. (2004) Time-dependent lethal body residues for the toxicity of pentachlorobenzene to *Hyalella azteca*. *Environ Toxicol Chem* 23(5):1335-1343
- Landrum, PF; Steevens, JA; McElroy, M; Gossiaux, DC; Lewis, JS; Robinson, SD. (2005) Time-dependent toxicity of dichlorodiphenyldichloroethylene to *Hyalella azteca*. *Environ Toxicol Chem* 24(1):211-218.
- Langmuir, D. (1997) *Aqueous environmental chemistry*. Upper Saddle River, NJ: Prentice-Hall.
- Langmuir, D; Chrostowski, P; Chaney, R; Vigneault, B. (2003) Issue paper on the environmental chemistry of metals. August. Available online at http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=379035.
- Langston, WJ. (1980) Arsenic in U.K. estuarine sediments and its availability to benthic organisms. *J Marine Biol Assn UK* 60:869B881.
- Lanno, RP; LeBlanc, S; Knight, B; Tymowski, R; Fitzgerald, DG. (1998) Application of body residues as a tool in the assessment of soil toxicity. In: Sheppard, S; Bembridge, J; Holmstrup, M; et al.; eds. *Advances in earthworm ecotoxicology*. Pensacola, FL: SETAC Press; pp. 41B53.
- Lanno, RP; McCarty, LS. (1997) Earthworm bioassays: Adopting techniques from aquatic toxicity testing. *Soil Biol Biochem* 29:693-697.
- Lanno, RP (ed). (2003) *Contaminated soils: from soil-chemical interactions to ecosystem management*. Pensacola, FL; SETAC Press; 427pp.
- Laperche, V; Logan, TJ; Gaddam, P; Traina, SJ. (1997) Effect of apatite amendments on plant uptake of lead from contaminated soil. *Environ Sci Technol* 31(10):2745B2753.
- Larison, JR; Likens, GE; Fitzpatrick, JW; Crock, JG. (2000) Cadmium toxicity among wildlife in the Colorado Rocky Mountains. *Nature* 406(6792):181B183.
- Laurie, SH; Manthey, JA. (1994) The chemistry and role of metal ion chelation in plant uptake processes. In: Manthey, JA; Crowley, DE; Luster, DG; eds. *Biochemistry of metal micronutrients in the rhizosphere*. Boca Raton, FL: Lewis Publishers; pp. 165B182.
- Leggett, RW. (1993) An age-specific kinetic model of lead metabolism in humans. *Environ Health Perspect* 101(1):598B616.
- LePoire, D; Arnish, J; Gnanapragasam, ES; Kamboj, S; Biwer, BM; Cheng, JJ; Yu, C; Chen, SY. (2000) Probabilistic modules for the RESRAD and RESRAD-build computer codes. NUREG/CR-XX ANL/EAD/TM-91. Argonne, IL: Argonne National Laboratory.
- Lindsay, WL. (1979) *Chemical equilibria in soils*. New York, NY: John Wiley & Sons; pp. 162–209.
- Lock, K; Janssen, CR. (2001) Modeling zinc toxicity for terrestrial invertebrates. *Environ Toxicol Chem* 20:1901-1908.
- Lofts, S; Tipping, E. (1998) An assemblage model for cation binding by natural particulate matter. *Geochim Cosmochim Acta* 62(15):2609B2625.
- Lukaski, HC. (1999) Chromium as a supplement. *Annual Rev Nutr* 19:279-302.
- Lund, W. (1990) The complexation of metal ions by humic substances in natural waters. In: Broekaert, JAC, Güçer, S; Adams, F; eds. *Metal speciation in the environment*. Nato ASI Series, Vol. G23. Berlin, Germany: Springer-Verlag; pp 43-55.

- Luoma, SN; Bryan, GW. (1978) Factors controlling the availability of sediment-bound lead to the estuarine bivalve *Scrobicularia plana*. *J Marine Biol Assn UK* 58:793B802.
- Luoma, SN; Johns, C; Fisher, NS; Steinberg, NA; Oremland, RS; Reinfelder, JR. (1992) Determination of selenium bioavailability to a benthic bivalve from particulate and solute pathways. *Environ Sci Technol* 26(3):485-491.
- Luoma, SN; Rainbow, PS. (2005) Why is metal bioaccumulation so variable? Biodynamics as a unifying concept. *Environ Sci Technol* 39(7), 1921–1931.
- Ma, H; Kim, SD; Cha, DK; Allen, HE. (1999) Effect of kinetics of complexation by humic acid on toxicity of copper to *Ceriodaphnia dubia*. *Environ Toxicol Chem* 18(5):828-837.
- MacDonald, DD; Carr, RS; Calder, FD; Long, ER; Ingersoll, CG. (1996) Development and evaluation of sediment quality guidelines for Florida coastal waters. *Ecotoxicol* 5:253-278.
- MacDonald, DD; Ingersoll, CG; Berger, TA. (2000) Development and evaluation of consensus-based sediment quality guidelines for freshwater ecosystems. *Arch Environ Contam Toxicol* 39(1):20B31.
- McCarty, LS. (1986) Relationship between aquatic toxicity QSARS and bioconcentration for some organic chemicals. *Environ Toxicol and Chem* 5(12):1071-1080.
- McCarty, LS; Mackay, D. (1993) Enhancing ecotoxicological modeling and assessment: body residues and modes of toxic action. *Environ Sci Technol* 27:1718(9)-1728.
- McLaughlin, MJ; Smolders, E. (2001) Background zinc concentrations in soil affect the zinc sensitivity of soil microbial processes: a rationale for a metalloregion approach to risk assessments. *Environ Toxicol Chem* 20: 2639-2643.
- Marr, JCA; Hansen, JA; Meyer, JS; Cacela, D; Podrabsky, T; Lipton, J; Bergman, HL. (1998) Toxicity of cobalt and copper to rainbow trout: application of a mechanistic model for predicting survival. *Aquatic Toxicol* 43(4):225-238.
- Marschner, H. (1995) Mineral nutrition of higher plants. 2nd ed. San Diego, CA: Academic Press.
- Marschner, H. (1998) Soil root interface: biological and biochemical processes. In: Huang, PM, ed. *Soil chemistry and ecosystem health*. Madison, WI. Soil Science Society of America; pp. 191B232.
- Mason, AZ; Jenkins, KD. (1995) Metal detoxification in aquatic organisms. In: Tessier, A; Turner, DR, eds. *Metal speciation and bioavailability in aquatic systems*. Chichester, UK: John Wiley & Sons; pp. 479B608.
- Mayer, LM; Schick, LL; Self, RFL; Jumars, PA; Findlay, RH; Chen, Z; Sampson, S. (1997) Digestive environments of benthic macroinvertebrate guts: enzymes, surfactants, and dissolved organic matter. *Marine Res* 55(4):785-812.
- Mayer, LM; Weston, DP; Bock, MJ. (2001) Benzo[a]pyrene and zinc solubilization by digestive fluids of benthic invertebrates: a cross-phyletic study. *Environ Toxicol Chem* 20:1890B1900.
- McDowell, LR. (2003) Minerals in animal and human nutrition. 2nd ed. Amsterdam: Elsevier.
- McGeer, JC; Brix, KV; Skeaff, JM; DeForest, DK; Brigham, SI; Adams, WJ; Green, A. (2003) Inverse relationship between bioconcentration factor and exposure concentration for metals: implications for hazard assessment of metals in the aquatic environment. *Environ Toxicol Chem* 22(5)1017B1037.
- McGeer, J; Henningsen, G; Lanno, R; Fisher, N; Sappington, K; Drexler, J. (2004) Issue paper on the bioavailability and bioaccumulation of metals. Available online at <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>.
- McGeer, JC; Playle, RC; Wood, CM; Galvez, F. (2000) A physiologically based biotic ligand model for predicting the acute toxicity of waterborne silver to rainbow trout in freshwaters. *Environ Sci Technol* 34(19):4199B4207.

- McGeer, JC; Szebedinszky, C; McDonald, DG; Wood, CM. (2002) The role of dissolved organic carbon in moderating the bioavailability and toxicity of Cu to rainbow trout during chronic waterborne exposure. *Comp Biochem Phys* 133:147-160.
- McGeer, JC; Wood, CM. (1998) Protective effects of water Cl⁻ on physiological responses to waterborne silver in rainbow trout. *Can J Fish Aquat Sci* 55(11):2447–2454.
- McGrath, SP. (1995) Chromium and nickel. In: Alloway, BJ; ed. *Heavy metals in soils*. London: Blackie Academic and Professional; pp. 152B178.
- McKinney, PE. (1999) Elemental mercury in the appendix: an unusual complication of a Mexican-American folk remedy. *J Toxicol Clin Toxicol* 37(1):103-107.
- McKone, TE. (1987) Human exposure to volatile organic compounds in household tap water: the indoor inhalation pathway. *Environ Sci Technol* 21:1194B1201.
- McLaughlin, MJ; Hamon, RE; Parker, DR; Pierzynski, GM; Smolders, E; Thornton, I; Welp, G. (2002) Soil chemistry. In: Fairbrother, A; Glazebrook, PW; Terazona, JV; eds. *Test methods to determine hazards of sparingly soluble metal compounds in soils*. Pensacola, FL: SETAC Press; pp. 5B16.
- McLaughlin, MJ; Smolders, E. (2001) Background zinc concentrations in soil affect the zinc sensitivity of soil microbial processes – A rationale for a metalloregion approach to risk assessments. *Environ Toxicol Chem* 20(11):2639B2643.
- Menzie-Cura & Associates, Inc.; TN&A, Inc. (2000) Development of a framework to address bioavailability issues in wildlife. Submitted to Randall Wentzel, U.S. EPA, National Center for Environmental Assessment, Washington, DC; EPA/630/P-02/003A.
- Meplan, C; Richard, MJ; Hainaut, P. (2000) Redox signalling and transition metals in the control of the p53 pathway. *Biochem Pharmacol* 59(1):25–33.
- Mertz, W. (1981) The essential trace elements. *Science* 213:1332B1338.
- Mertz, W. (1993) Chromium in human nutrition: a review. *J Nutr* 123(4):626-633.
- Mertz, W. (1995) Risk assessment of essential trace elements: new approaches to setting recommended dietary allowances and safety limits. *Nutr Rev* 53(7):179-185.
- Meyer, J. (2002) The utility of the terms “bioavailability” and “bioavailable fraction” for metals. *Marine Environ Res* 53(4):417B423.
- Mills, WB; Porcella, DV; Unga, MJ; Gherini, SA; Summers, KV; Lingsung, M; Rupp, GL; Bowie, GL; Haith, DA. (1985) Water quality assessment: a screening procedure for toxic and conventional pollutants in surface and ground water. Part 1. EPA-600-6-85-002a.
- Morrison, HA; Whittle, DM; Haffner, GD. (2000) The relative importance of species invasions and sediment disturbance in regulating chemical dynamics in western Lake Erie. *Ecol Modeling* 125(2-3):279B294.
- Mowat, FS; Bundy, KJ. (2002) Experimental and mathematical/computational assessment of the acute toxicity of chemical mixtures from the Microtox assay. *Adv Environ Res* 6(4):547B558.
- Moya, J; Howard-Reed, C; Corsi, RL. (1999) Volatilization of chemicals from tap water to indoor air from contaminated water used for showering. *Environ Sci Technol* 33(14):2321B2327.
- Mudroch, A; Azcue, JM; Mudroch, P. (1997) *Manual of physico-chemical analysis of aquatic sediments*. Boca Raton, FL: Lewis Publishers.
- Mudroch, A; Azcue, JM; Mudroch, P. (1999) *Manual of bioassessment of aquatic sediment quality*. Boca Raton, FL: Lewis Publishers.

NAS/IOM (National Academy of Sciences/Institute of Medicine). (2000) Dietary reference intakes: applications in dietary assessment. Food and Nutrition Board, Institute of Medicine, Washington, DC.

NAS/IOM (National Academy of Sciences/Institute of Medicine). (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. A Report of The Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Uses of Dietary Reference Intakes, and The Standing Committee on The Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. Washington, DC: National Academ Press.

NAS/IOM (National Academy of Sciences/Institute of Medicine). (2003) Dietary reference intakes: guiding principles for nutrition labeling and fortification. Food and Nutrition Board, Institute of Medicine, Washington, DC.

NAS/NRC (National Academy of Sciences/National Research Council). (1980) Mineral tolerance of domestic animals. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1983) Risk assessment in the federal government: managing the process. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1988) Complex mixtures – Methods for in vivo toxicity testing. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1994a) Nutritional requirements of poultry. 9th rev. ed. National Academy of Sciences, Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1994b) Science and judgment in risk assessment. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1996) Understanding risk: informing decisions in a democratic society. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (1999) Arsenic in drinking water. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (2000) Toxicological effects of methyl mercury. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (2001) Arsenic in drinking water: 2001 update. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (2002) Bioavailability of contaminants in soils and sediments: processes, tools, and applications. Washington, DC: National Academ Press.

NAS/NRC (National Academy of Sciences/National Research Council). (2006) Human biomonitoring for environmental chemicals. Washington, DC: National Academ Press.

Newman, MC; Diamond, GL; Menzie, C; Moya, J; Nriagu, J. (2004) Issue paper on metal exposure assessment. Available online at <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>.

Newman, MC; McCloskey, JT. (1996) Predicting relative metal toxicity and interactions of divalent metal ions: microtox bioluminescence assay. *Environ Toxicol Chem* 15(3):275B281.

Ng, JC; Kratzmann, SM; Qi, L; Crawley, H; Chiswell, B; Moore, MR. (1998) Speciation and absolute bioavailability: risk assessment of arsenic contaminated sites in a residential suburb in Canberra. *Analyst* 123(5):889B892.

Norwood, WP; Borgmann, U; Dixon, DG; Wallace, A. (2003) Effects of metal mixtures on aquatic biota: a review of observations and methods. *Hum Ecol Risk Assess* 9(4):795B811.

- Nott, JA; Nicolaidou, A. (1990) Mediterranean pollution from a ferro-nickel smelter: differential uptake of metals by some gastropods. *Marine Pollut Bull* 21(3):137B143.
- NTP (National Toxicology Program). 2002. 10th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, Washington, DC.
- Nyffeler, UP; Santschi, PH; Li, Y-H. (1986) The relevance of scavenging kinetics to modeling of sediment water interactions in natural waters. *Limnol Oceanogr* 31(2):277B292.
- Oberdorster, G. (1992) Pulmonary deposition, clearance and effects of inhaled soluble and insoluble cadmium compounds. In: Nordberg, GF; Herber, RFM; Alessio, L; eds. *Cadmium in the human environment: toxicity and carcinogenicity*. Lyon, France: IARC; pp. 189-204.
- O'Flaherty, EJ. (1995) Physiologically based models for bone-seeking elements. V: Lead absorption and disposition in childhood. *Toxicol Appl Pharmacol* 131(2):297B308.
- O'Flaherty, EJ. (1998) Physiologically based models of metal kinetics. *Crit Rev Toxicol* 28(3):271B317.
- O'Rourke, MK; van de Water, PK; Jin, S; Rogan, SP; Weiss, AD; Gordon, SM; Moschandreas, DM; Lebowitz, MD. (1999) Evaluations of primary metals from NHEXAS Arizona: distributions and preliminary exposures. *J Exposure Anal Environ Epidemiol* 9(5):435B445.
- Ownby, DR; Newman, MC. (2003) Advances in quantitative ion character-activity relationships (QICARs): using metal-ligand binding characteristics to predict metal toxicity. *Quant Struct Act Relat (QSAR) Comb Sci* 22(2):241B246.
- Paquin, PR; DiToro, DM; Santore, RC; Trivedi, D; Wu, KB. (1999) A biotic ligand model of the acute toxicity of metals. III: application to fish and daphnia exposure to silver. U.S. EPA Office of Water, Office of Research and Development.
- Paquin, PR; Gorsuch, JW; Apte, S; Batley, GE; Bowles, KC; Campbell, PG; Delos, CG; Di Toro, DM; Dwyer, RL; Galvez, F; Gensemer, RW; Goss, GG; Hostrand, C; Janssen, CR; McGeer, JC; Naddy, RB; Playle, RC; Santore, RC; Schneider, U; Stubblefield, WA; Wood, CM; Wu, KB. (2002a) The biotic ligand model: a historical overview. Special issue: The biotic ligand model for metals. *Current research, future directions, regulatory implications. Comp Biochem Physiol C Toxicol Pharmacol* 133(1-2):3-35.
- Paquin, PR; Zoltay, V; Winfield, RP; Wu, KB; Mathew, R; Santore, RC; Di Toro, DM. (2002b) Extension of the biotic ligand model of acute toxicity to a physiologically-based model of the survival time of rainbow trout (*Oncorhynchus mykiss*) exposed to silver. *Comp Biochem Physiol (C)* 133(1-2):305B343.
- Paquin, PR; Santore, RC; Farley, K; Di Toro, DM; Wu, KB; Mooney, KG; Winfield, RP. (2003) Metals in aquatic systems: A review of exposure, bioaccumulation, and toxicity models (aquatic metals). Pensacola, FL: SETAC Press.
- Parker, DR; Pedler, JF; Ahnstrom, ZAS; Resketo, M. (1997) Reevaluating the free ion activity model of trace metal availability to higher plants. In: Ando, T; Fujita, K; Mae, T; et al.; eds. *Plant nutrition for sustainable food production and environment*. Dordrecht, Netherlands: Kluwer; pp. 107B112.
- Parkhurst, DL; Thorstenson, DC; Plummer, LN. (1980) PHREEQEBA computer program for geochemical calculations. U.S. Geological Survey, Water-Resources Investigations Report 8B96, 210 pp.
- Paustenbach, DJ. (2000) The practice of exposure assessment: a state-of-the-art review. *J Toxicol Environ Health (part B)* 3(3):179B291.
- Pearson, RG. (1973) *Hard and soft acids and bases*. Stroudsburg, PA: Dowden, Hutchinson & Ross.
- Peijnenburg, WJGM; Baerselman, R; De Groot, AC; Jager, T; Posthuma, L; Van Veen, RPM. (1999a) Relating environmental availability to bioavailability: soil-type dependent metal accumulation in the oligochaete *Eisenai andrei*. *Ecotoxicol Environ Saf* 44(3):294B310.

- Peijnenburg, WJGM; Posthuma, L; Zweekers, PGPC; Baerselman, R; de Groot, AC; Van Veen, RPM; Jager, T. (1999b) Prediction of metal bioavailability in Dutch field soils for the oligochaete *Enchytraeus crypticus*. *Ecotoxicol Environ Saf* 44(2):170B186.
- Phalen, RF; Oldham, MJ; Beaucage, CB; Crocker, TT; Mortensen, Jd. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. *Anat Rec* 212(4):368B380.
- Picciano, MF. (1996) Pregnancy and lactation. In: Ziegler, EE; Filer, Jr, LJ; eds. *Present knowledge in nutrition*. 7th ed. Washington, DC: ILSI Press; pp. 384B395.
- Pickering, WF. (1986) Metal ion speciation in soils and sediments (a review). *Ore Geology Rev* 1(1):83-146.
- Plunkett, LM; Turnball, D; Rodricks, JV. (1992): Differences between adults and children affecting exposure assessment. In: Guzelian, PS; Henry, CJ; Olin, SS; eds. *Similarities and differences between children and adults: implications for risk assessment*. Washington, DC: International Life Sciences Institute Press; pp. 79-94.
- Pontifex, AH; Garg, AK. (1985) Lead poisoning from an Asian Indian folk remedy. *CMAJ* 133(12):1227-8.
- Posthuma, L; Baerselman, R; Van Veen, RPM; Dirven-Van Breemen, EM. (1997) Single and joint toxic effects of copper and zinc on reproduction of *Enchytraeus crypticus* in relation to sorption of metals in soils. *Ecotoxicol Environ Saf* 38(2):108B121.
- Prozialeck, WC; Grunwald, GB; Dey, PM; Reuhl, KR; Parrish, AR. (2002) Cadherins and NCAM as potential targets in metal toxicity. *Toxicol Appl Pharmacol* 182(3):255-265.
- Rainbow, PS. (2002) Trace metal concentrations in aquatic invertebrates: why and so what? *Environ Pollut* 120(3):497B507.
- Reinfelder, JR; Fisher, NS. (1994a) The assimilation of elements ingested by marine planktonic bivalve larvae. *Limnol Oceanogr* 39(1):12-20.
- Reinfelder, JR; Fisher, NS. (1994b) Retention of elements absorbed by juvenile fish (*Menidia menidia*, *Menidia beryllina*) from zooplankton prey. *Limnol and Oceanogr* 39(8):1783-1789.
- Reinfelder, JR; Fisher, NS; Luoma, SN; Nichols, JW; Wang, WX. (1998) Trace element trophic transfer in aquatic organisms: a critique of the kinetic model approach. *Sci Total Environ* 219(213):117B135.
- Reuther, R. (1999) Trace metal speciation in aquatic sediments: methods, benefits, and limitations. In: *Manual of bioassessment of aquatic sediment quality*. Mudroch, A; Azcue, JM; Mudroch, P, eds. Boca Raton, FL: Lewis Publishers; pp. 1B54.
- Richardson, GM. (2002) Natural sources and emissions of elements to the atmosphere. International Council on Mining and Metals. No. 11, February. Available online at http://www.icmm.com/uploads/44Fact11_final2.pdf.
- Roditi, HA; Fisher, NS; Sañudo-Wilhelmy, SA. (2000) Field testing a metal bioaccumulation model for zebra mussels. *Environ Sci Technol* 34(13):2817-2825.
- Roesijadi, G. (1992) Metallothioneins in metal regulation and toxicity in aquatic animals. *Aquat Toxicol* 22(2):81B114.
- Roy, I; Hare, L. (1999) Relative importance of water and food as Cd sources to the predatory insect *Sialis vlata* (Megaloptera). *Can J Fish Aquat Sci* 56(7):1143B1149.
- Ryan, PB; Scanlon, KA; MacIntosh, DL. (2001) Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. *Environ Health Perspect* 109(2):121B129.
- SAB (Science Advisory Board). (2006) Memorandum from Dr. M. Granger Morgan, Chair EPA Science Advisory Board and Dr. Deborah L. Swackhamer, Chair, Metals Risk Assessment Framework Review Panel, EPA Science

Advisory Board to The Honorable Stephen L. Johnson Administrator U.S. Environmental Protection Agency.
Subject: Review of EPA's Draft Framework for Inorganic Metals Risk Assessment. Dated January 25, 2006. EPA-SAB-06-002.

Salocks, C; Hathaway, T; Ziarkowski, C; Walker, W. (1996) Physical characterization, solubility and potential bioavailability of arsenic in tailings from a former gold mine. *Toxicologist* 16:48.

Sample, BE; Arenal, CA. (2001) Development of literature-based bioaccumulation models for terrestrial arthropods. Platform presentation at the November 2001 SETAC Meeting, Baltimore, MD.

Sample, BE; Aplin, MS; Efrogmson, RE; Suter, GW, II; Welsh, CJE. (1997) Methods and tools for estimation of the exposure of terrestrial wildlife to contaminants. Oak Ridge National Laboratory, Oak Ridge, TN; ORNL/TM-13391.

Sample, BE; Beauchamp, JJ; Efrogmson, R; Suter, GW, II; Ashwood, TL. (1998b) Development and validation of bioaccumulation models for small mammals. Oak Ridge National Laboratory, Lockheed Martin Energy Systems Environmental Restoration Program, Oak Ridge, TN; ES/ER/TM-219.

Sample, BE; Beauchamp, JJ; Efrogmson, R; Suter, GW, II. (1999) Literature-derived bioaccumulation models for earthworms: development and validation. *Environ Toxicol Chem* 18(9):2110B2120.

Sample, BE; Beauchamp, JJ; Efrogmson, RA; Suter, GW, II; Ashwood, TL. (1998a) Development and validation of bioaccumulation models for earthworms. Prepared for the U.S. Department of Energy under Contract DE-AC05-84OR21400. Code EW 20. Oak Ridge National Laboratory, Oak Ridge, TN; ES/ER/TM-220.

Santore, RC; Di Toro, DM; Paquin, PR. (2001) Biotic ligand model of the acute toxicity of metals: 2. application to acute copper toxicity in freshwater fish and *Daphnia*. *Environ Toxicol Chem* 20(10):2397B2402.

Santore, RC; Driscoll, CT. (1995) The CHESS model for calculating chemical equilibria in soils and solutions. Chemical equilibrium and reaction models. Soil Science Society of America, American Society of Agronomy, Special Publication 42, Madison, WI.

Santschi, PH; Nyffeler, UP; Li, Y-H; O'Hara, P. (1986) Radionuclide cycling in natural waters: relevance of scavenging kinetics. In: Sly, PG; ed. *Sediments and water interactions*. Springer Verlag, New York, NY; ch 17, pp. 183B191.

Sauvé, S; Dumestre, A; McBride, MB; Hendershot, WH. (1998) Derivation of soil quality criteria using predicted chemical speciation of Pb²⁺ and Cu²⁺. *Environ Toxicol Chem* 17(8):1481B1489.

Saxe, JK; Impellitteri, CA; Peijnenburg, WJGM; Allen, HE. (2001) Novel model describing trace metal concentrations in the earthworm, *Eisenia andrei*. *Environ Sci Technol* 35(22):4522B4529.

Schacklette, HT; Boerngen, JG. (1984) Element concentrations in soils and other surficial materials of the conterminious United States. U.S. Geol Survey Prof Paper 1270, pg. 105.

Schecher, WD; McAvoy, DC. (1994) MINEQL+: A chemical equilibrium program for personal computers (version 3.01). Environmental Research Software, Hallowell, ME.

Schecher, WD; McAvoy, DC. (2001) MINEQL+ - A chemical equilibrium modelling system, version 4.5 for windows user's manual. Environmental Research Software, Hallowell, ME, USA.

Schnoor, JL; Sato, C; McKechnie, D; Sahoo, D. (1987) Processes, coefficients, and models for simulating toxic organics and heavy metals in surface waters. EPA-600-3-87-015.

Schoof, RA; Eickhoff, J; Yost, LJ; Crecelius, EA; Cragin, DW; Meacher, DM; Menzel, DB. (1999a) Dietary exposure to inorganic arsenic. pp. 81-88. In: *Proceedings of the third international conference on arsenic exposure and health effects*. Chappell, WR; Abernathy, CO; Calderon, RL, eds. Amsterdam:Elsevier Science Ltd.

- Schoof RA, Eickhoff J, Yost LJ, Crecelius EA, Cragin DW, Meacher DM, et al. 1999. Dietary exposure to inorganic arsenic. In: Arsenic Exposure and Health Effects (Chappell WR, Abernathy CO, Calderon RL, eds). Amsterdam:Elsevier, 81–88.
- Schroeder, WH; Munthe, J. (1998) Atmospheric mercury – an overview. *Atmos Environ* 32(5):809-822.
- Scott-Fordsmand, JJ; Odegard, K. (2002) Multi-element analysis as a marker of metal exposure in *Eisenia veneta*. Poster presentation. 7th International Symposium on Earthworm Ecology, September 1B6, Cardiff, Wales.
- Seebaugh, DR; Wallace, WG. (2004) Importance of metal-binding proteins in the partitioning of Cd and Zn as trophically available metal (TAM) in the brine shrimp *Artemia franciscana*. *Marine Ecol Prog Ser* 272:215B230.
- Seigneur, C; Constantinou, E. (1995) Chemical kinetic mechanism for atmospheric chromium. *Environ Sci Technol* 29(1):222B231.
- Sharma, A; Srivastava, PC; Johri, BN. (1994) Contribution of VA Mycorrhiza to zinc uptake in plants. In: Manthey, JA; Crowley, DE; and D.G.; eds. *Biochemistry of metal micronutrients in the rhizosphere*. Boca Raton, FL: Lewis Publishers; pp. 111B124.
- Sharma, SS; Schat, H; Vooijs, R; Van Heerwaarden, LM. (1999) Combination toxicology of copper, zinc and cadmium in binary mixtures: Concentration-dependent antagonistic, nonadditive, and synergistic effects on root growth in *Silene vulgaris*. *Environ Toxicol Chem* 18(2):348–355.
- Smit, E. (1997) Field relevance of the *Folsomia candida* soil toxicity test. Ph.D. dissertation. Vrije Universiteit, Amsterdam.
- Smolders, E; McGrath, SP; Lombi, E; McLaughlin, MJ; Rutgers, M; Fairbrother, A; Van der Vliet, L; Hale, B. (2006) Hazard assessment of metals and metal compounds in terrestrial systems based on persistency, bioaccumulation, and toxicity In: Adams, WJ; et al.; eds. *Hazard identification approach for metals and inorganic metal substances*. Pensacola, FL: SETAC Press.
- Spehar, RL; Fiandt, JT. (1986) Acute and chronic effects of water quality criteria-based metal mixtures on three aquatic species. *Environ Toxicol Chem* 5:917B931.
- SRWG (Science and Research Working Group of the Non-Ferrous Metals Consultative Forum on Sustainable Development). (2002) Risk assesment of non-ferrous metals and sustainable development. Available online at http://www.nfmsd.org/wg_research/docs/RAcombined1002.pdf#search=%22Risk%20assessment%20of%20non-ferrous%20metals%20and%20sustainable%20development%22%22.
- Stauber, JL; Florence, TM; Gulson, BL; Dale, LS. (1994) Percutaneous absorption of inorganic lead compounds. *Sci Total Environ* 145(1-2):55-70.
- Stern, AH. (1996) Derivation of a target concentration of Pb in soil based on elevation of adult blood pressure. *Risk Anal* 16(2):201B210.
- Stewart, GM; Fisher, NS. (2003) Bioaccumulation of polonium-210 in marine copepods. *Limnol Oceano* 48(3):1193-1201.
- Stoica, A; Katzenellenbogen, BS; Martin, MB. (2000) Activation of estrogen receptor-alpha by the heavy metal cadmium. *Mol Endocrinol* 14(4):545-53.
- Stumm, W; Morgan, JJ. (1970) *Aquatic chemistry. An introduction emphasizing chemical equilibria in natural waters*. New York, NY: John Wiley & Sons.
- Stumm, W; Morgan, JJ. (1996) *Aquatic chemistry*. 3rd ed. New York, NY: John Wiley & Sons.
- Suedel, BC; Boracsek, JA; Peddicord, RK; Clifford, PA; Dillon, TM. (1994) Trophic transfer and biomagnification potential of contaminants in aquatic ecosystems. *Rev Environ Toxicol Chem* 136:21B89.

- Sumner, ME. (ed). (1999) Handbook of soil science. Boca, Raton, FL: CRC Press.
- Sunde, RA; O'Dell, BL. (1997) Handbook of Nutritionally Essential Mineral Elements. New York, NY: Marcel Dekker, Inc.
- Suter, GW, II. (1993) Ecological risk assessment. Boca Raton, FL: Lewis Publishers.
- Tack, FMG; Verloo, MG. (1999) Single extractions versus sequential extraction for the estimation of heavy metal fractions in reduced and oxidised dredged sediments. *Chem Spec & Bioavail* 11(2):43-50.
- Templeton, DM; Ariese, F; Cornelis, R.; Danielson, LG; Muntau, H; Van Leeuwen, HP; Lobinski, R. (2000) Guidelines for terms related to chemical speciation and fractionation of elements. Definitions, structural aspects, and methodological approaches. *Pure Appl Chem* 72(8):1453B1470.
- Tessier, A. (1992) Sorption of trace elements on natural particles in oxic environments . In: Buffle, J; Van Leeuwen, HP; eds. *Environmental particles*. Boca Raton, FL: Lewis Publishers; pp. 425B453.
- Tessier, A; Campbell, PGC; Bisson, M. (1979) Sequential extraction procedure for the speciation of particulate trace metals. *Anal Chem* 51(7):844B851.
- Tessier, A; Campbell, PGC; Auclair, JC; Bisson, M. (1984) Relationships between the partitioning of trace metals in sediments and their accumulation in the tissues of the freshwater mollusc *Elliptio complanata* in a mining area. *Can J Fish Aquat Sci*, 41:1463B1472.
- Tessier, A; Carignan, R; Dubreuil, B; Rapin, F. (1989) Partitioning of zinc between the water column and the oxic sediments in lakes. *Geochim Cosmochim Acta* 53(7):1511B1522.
- Tessier, A; Couillard, Y; Campbell, PGC; Auclair, JC. (1993) Modeling Cd partitioning in oxic lake sediments and Cd concentrations in the freshwater bivalve *Anodonta grandis*. *Limnol and Oceano*, 38(1):1B17.
- Thomas, KW; Pellizzari, ED; Berry, MR. (1999) Population-based dietary intakes and tap water concentrations for selected elements in the EPA Region V National Exposure Assessment Survey (NHEXAS). *J Exp Anal Environ Epidem* 9(5):402B413.
- Tipping, E. (1994) WHAM: a chemical equilibrium model and computer code for waters, sediments, and soils incorporating a discrete site/electrostatic model of ion-binding by humic substances. *Computers & Geoscience* 20:973B1023.
- Tomerlin, JR; Berry, MR; Tran, NL; Chew, S; Peterson, BJ; Tucker, KD; Fleming, KH. (1997) Development of a dietary exposure potential model for evaluating dietary exposure to chemical residues in food. *J Exp Anal Environ Epidem* 7(1):81B101.
- Trotter, RJ. II. (1985) Greta and Azarcon: a survey of episodic lead poisoning from a folk remedy. *Hum Org* 44(1): 64-72.
- Tsuda, T; Inoue, T; Kojima, Aoki, S. (1995) Market basket and duplicate portion estimation of dietary intakes of cadmium, mercury, arsenic, copper, manganese, and zinc by Japanese adults. *JAOAC Internat* 78(6):1363B1368.
- Tye, AM; Young, SD; Crout, NMJ; Zhang, H; Preston, S; Barbosa-Jefferson, VL; Davison, W; McGrath, SP; Paton, GI; Kilham, K; Resende, L. (2003) Predicting the activity of Cd²⁺ and Zn²⁺ in soil pore water from the radio-labile metal fraction. *Geochim Cosmochim Acta* 67(3):375B385.
- Tyler, G; Olsson, T. (2001a) Concentrations of 60 elements in the soil solution as related to the soil acidity. *Eur J Soil Sci* 52(1):151B165.
- Tyler, G; Olsson, T. (2001b) Plant uptake of major and minor mineral elements as influenced by soil acidity and liming. *Plant Soil* 230(2):307B321.

Ullrich, SM; Tanton, TW; Abdrashitova, SA. (2001) Mercury in the aquatic environment: a review of factors affecting methylation. *Crit Rev Environ Sci Tech* 31(3):241B293.

U.S. DHHS (Department of Health and Human Services). (1996) National Center for Health Statistics. Third National health and nutrition examination survey, 1988-1994, NHANES III individual foods data file from the dietary recall (CD-ROM). Public use data file documentation catalog number 76700. Hyattsville, MD.

U.S. DOE (Department of Energy). 2001. User's manual for RESRAD, version 6. ANL/EAD-4. Argonne National Laboratory, Argonne, IL.

U.S. EPA (Environmental Protection Agency). (1986) Guidelines for the health risk assessment of chemical mixtures. Risk Assessment Forum. Washington, DC. Federal Register 51(185):34014-34025. Available online at <http://epa.gov/ncea/raf>.

U.S. EPA (Environmental Protection Agency). (1987) Selection criteria for mathematical models used in exposure assessments: surface water models. Office of Health and Environmental Assessment, Washington, DC; EPA-600/8-87-042.

U.S. EPA (Environmental Protection Agency). (1987) Selection criteria for mathematical models used in exposure assessments: surface water models. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/042.

U.S. EPA (Environmental Protection Agency). (1989a) Exposure factors handbook. Office of Health and Environmental Assessment, Washington, DC; EPA/600/8-89/043.

U.S. EPA (Environmental Protection Agency). (1989b) Rapid bioassessment protocols for use in streams and rivers: benthic macroinvertebrates and fish. Washington, DC; EPA 440/4-89/001.

U.S. EPA (Environmental Protection Agency). (1990) Methods for derivation of inhalation reference concentration and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Cincinnati, OH; Office of Research and Development, Washington, DC. EPA/600/8-90/066F.

U.S. EPA (Environmental Protection Agency). (1991) Guidelines for developmental toxicity risk assessment. Risk Assessment Forum, Washington, DC. Federal Register 56(234):63798-63826. Available online at <http://epa.gov/ncea/raf>.

U.S. EPA (Environmental Protection Agency). (1992a) Framework for ecological risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-92/001.

U.S. EPA (Environmental Protection Agency). (1992b) Ground water issue: behavior of metals in soils. Office of Solid Waste and Emergency Response, Washington, DC; EPA 540-S-92-018.

U.S. EPA (Environmental Protection Agency). (1992c) Guidelines for exposure assessment. Risk Assessment Forum, Washington, DC. Federal Register 57(104):22888-22938. Available online at <http://epa.gov/ncea/raf>.

U.S. EPA (Environmental Protection Agency). (1994a) Guidance manual for the integrated exposure uptake biokinetic model for lead in children. Office of Emergency and Remedial Response, Washington, DC; EPA/540/R-93/081. Available from the National Technical Information Services, Springfield, VA; PB93-963510.

U.S. EPA (Environmental Protection Agency). (1994b) Interim guidance on determination and use of water-effect ratios for metals. Office of Water, Office of Science and Technology, Washington, DC. EPA-823-B-94-001.

U.S. EPA (Environmental Protection Agency). (1994c) Water quality standards handbook, 2nd ed., appendix L: interim guidance on determination and use of water effect ratios for metals. Office of Water, Washington, DC; EPA-823-B-94-005a.

U.S. EPA (Environmental Protection Agency). (1996a) Review of the national ambient air quality standards for particulate matter; policy assessment of scientific and technical information. Office of Air Quality Planning and Standards Staff Paper. Office of Air Quality Planning and Standards, Washington, DC; EPA-452/R-96-013.

U.S. EPA (Environmental Protection Agency). (1996b) Recommendations of the technical review workgroup for lead for an approach to assessing risks associated with adult exposures to lead in soil. Office of Solid Waste and Emergency Response, Washington, DC; EPA 540 R 03 001.

U.S. EPA (Environmental Protection Agency). (1997a) Compendium of tools for watershed assessment and TMDL development. Office of Wetlands, Oceans, and Watersheds, Washington, DC; EPA-841-8-97-006.

U.S. EPA (Environmental Protection Agency). (1997b) Mercury study report to Congress. Office of Air and Radiation. Washington, DC; Available online at <http://www.epa.gov/mercury/report.html>.

U.S. EPA (Environmental Protection Agency). (1997c) Air quality criteria for particulate matter. Volume I of III. Office of Research and Development, Washington, DC; EPA/600/P 95/001aF.

U.S. EPA (Environmental Protection Agency). (1997d) The incidence and severity of sediment contamination in surface waters of the United States. Vol 1: national sediment quality survey. Office of Water, Washington, DC; EPA 823-R-97-006.

U.S. EPA (Environmental Protection Agency). (1997e) Exposure factors handbook. National Center for Environmental Assessment, Washington, DC; EPA/600/P-95/002Fc. Available online at <http://www.epa.gov/ncea/exposfac.htm>.

U.S. EPA (Environmental Protection Agency). (1998a) Guidelines for ecological risk assessment. Risk Assessment Forum, Washington, DC; Federal Register 63(93):26846-26924. Available online at <http://www.epa.gov/ncea/raf>.

U.S. EPA (Environmental Protection Agency). (1998b) Human health risk assessment protocol for hazardous waste combustion facilities. Office of Solid Waste and Emergency Response, Washington, DC; EPA 530-D-98:001.

U.S. EPA (Environmental Protection Agency). (1998c) Guidelines for neurotoxicity risk assessment. Risk Assessment Forum, Washington, DC. Federal Register 63(93):26926-26954. Available online at <http://www.epa.gov/ncea/raf>.

U.S. EPA (Environmental Protection Agency). (1998d) Toxicological review of beryllium and compounds in support of summary information on IRIS. National Center for Environmental Assessment, Washington, DC; EPA 635-R-98-008.

U.S. EPA (Environmental Protection Agency) (1999a) Understanding variation in partition coefficient, K_d, values. Office of Air and Radiation, Washington, DC; EPA 402-R-99-004A&B.

U.S. EPA (Environmental Protection Agency). (1999b) Compendium of methods for the determination of inorganic compounds in ambient air. Office of Research and Development, Washington, DC; EPA/625/R-96/010.

U.S. EPA (Environmental Protection Agency). (2000a) Region 10 guidance for Superfund human health risk assessment: interim. EPA Region 10, Seattle, WA.

U.S. EPA (Environmental Protection Agency). (2000b) Supplementary guidance for conducting health risk assessment of chemical mixtures. National Center for Environmental Assessment, Washington, DC; EPA/630/R-00/002.

U.S. EPA (Environmental Protection Agency). (2000c) Science Policy Council handbook: Risk characterization. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-00-002. Available online at <http://www.epa.gov/OSA/spc>.

U.S. EPA (Environmental Protection Agency). (2001a) Description and evaluation of atmospheric mercury simulation using the CMAQ Model. National Exposure Research Library, Research Triangle Park, NC; EPA/600/J 03/227.

U.S. EPA (Environmental Protection Agency). (2001b) ECO update; The role of screening-level risk assessments and refining contaminants of concern in baseline ecological risk assessments. Office of Solid Waste and Emergency Response. Washington, DC; OSWER 9345.0-14; EPA-540/F-01-014.

- U.S. EPA (Environmental Protection Agency). (2002a) A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/002F, 2002. Available online at <http://www.epa.gov/ncea/raf>.
- U.S. EPA (Environmental Protection Agency). (2002b) Child-specific exposure factors handbook. interim report National Center for Environmental Assessment, Office of Research and Development, Washington, DC; EPA-600-P-00-002B. Available online at <http://www.epa.gov/ncea>.
- U.S. EPA (Environmental Protection Agency). (2003a) Human health research strategy. Office of Research and Development, Washington, DC. Available online at http://www.epa.gov/nheerl/humanhealth/HHRS_final_web.pdf.
- U.S. EPA (Environmental Protection Agency). (2003b) Draft final guidelines for carcinogen risk assessment. (external review draft). Risk Assessment Forum, Washington, DC; EPA/630/P-03/001A, NCEA-F-0644A. Available online at <http://www.epa.gov/ncea/raf/cancer2003.htm>.
- U.S. EPA (Environmental Protection Agency). (2003c) Guidance for the development of ecological soil screening levels. Office of Solid Waste and Emergency Response, Washington, DC; OSWER Directive 92857-55.
- U.S. EPA (Environmental Protection Agency). (2003d) Literature review and evaluation of the atmospheric persistence of air toxic compounds; Internal EPA Report. Research Triangle Park, NC; EPA/600/X-03/011. Available online at http://www.epa.gov/nerl/research/2003/g1_2.html.
- U.S. EPA (Environmental Protection Agency). (2003e) Framework for cumulative risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-02/001F.
- U.S. EPA (Environmental Protection Agency). (2004) Air quality criteria for particulate matter (external review draft). National Center for Environmental Assessment. Washington, DC. Available online at <http://cfpub2.epa.gov/ncea/cfm/partmatt.cfm>.
- U.S. EPA (Environmental Protection Agency). (2005a) Guidelines for carcinogen risk assessment 2005 guidelines and 2005 supplementary guidance. Risk Assessment Forum, Washington, DC. Federal Register 70(66):17765-17817. Available online at <http://www.epa.gov/cancerguidelines>.
- U.S. EPA (Environmental Protection Agency). (2005b) Supplemental guidance for assessing susceptibility from early life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at <http://www.epa.gov/cancerguidelines>.
- U.S. EPA (Environmental Protection Agency). (2006a) Estimation of relative bioavailability of lead in soil and soil-like materials using in vivo and in vitro methods. Office of Solid Waste and Emergency Response, Washington, DC; OSWER 9285.7-77.
- U.S. Environmental Protection Agency (EPA). (2006b) A framework for assessing health risks of environmental exposures to children. National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/093F. Available from the National Technical Information Service, Springfield, VA, and online at <http://www.epa.gov/ncea>.
- U.S. FDA (Food and Drug Administration). (2001) Total diet survey. Center for Food Safety and Applied Nutrition, Office of Plant and Dairy Foods and Beverages, Washington, DC. Data summaries available online at <http://vm.cfsan.fda.gov/~comm/tds-toc.html>.
- Van Straalen, NM. (1996) Critical body concentrations: their use in bioindication. In: Van Straalen, NM; Krivolutsky, DA; eds. Bioindicator systems for soil pollution. Dordrecht, The Netherlands: Kluwer; pp. 5-16.
- Van Straalen, NM; Løkke, H. (1997) Ecological Risk Assessment of Contaminants in Soil. London: Chapman and Hall; pp. 333.
- Van Wensem, J; Vegter, JJ; Van Straalen, NM. (1994) Soil quality criteria derived from critical body concentrations of metals in soil invertebrates. *Appl Soil Ecol* 1(2):185B191.

- Veith, GD; Call, DJ; Brooke, L. (1983) Structure-toxicity relationships for the fathead minnow, *Pimephales promelas*: Narcotic industrial chemicals. *Can J Fish Aquatic Sci* 40:743-748.
- Wallace, WG; Lopez, GR. (1996) Relationship between subcellular cadmium distribution in prey and cadmium trophic transfer to a predator. *Estuaries* 19(4):923B930.
- Wallace, WG; Lopez, GR; Levinton, JS. (1998) Cadmium resistance in an oligochaete and its effect on cadmium trophic transfer to an omnivorous shrimp. *Marine Ecol Prog Ser* 172:225B237.
- Wallace, WG; Lee, BG; Luoma, SN. (2003) Subcellular compartmentalization of Cd and Zn in two bivalves. I. Significance of metal-sensitive fractions (MSF) and biologically detoxified metal (BDM). *Marine Ecol Prog Ser* 249:183-197.
- Wallace, WG; Luoma, SN. (2003) Subcellular compartmentalization of Cd and Zn in two bivalves. II. Significance of trophically available metal (TAM). *Marine Ecol Prog Ser* 257:125-137.
- Wallach, S. (1985) Clinical and biochemical aspects of chromium deficiency. *J Am College Nutr* 4(1):107-120.
- Wang, W-X; Fisher, NS; Luoma, SN. (1996) Kinetic determinations of trace element bioaccumulation in the mussel *Mytilus edulis*. *Marine Ecol. Prog Ser* 140:91-113.
- Wang, XL. (2002) Interactions of trace metals and different marine food chains. *Marine Ecol Prog Ser* 243:295B309.
- Wang, XL; Fisher, NS. (1996) Assimilation of trace elements and carbon by the mussel *Mytilus edulis*: effects of food composition. *Limnol Oceanog* 41(2):197-207.
- Wang, XL; Fisher, NS. (1999) Assimilation efficiencies of chemical contaminants in aquatic invertebrates: a synthesis. *Environ Toxicol Chem* 18(9):2034B2045.
- Wang, XL; Zauke, G-P. (2004) Size-dependent bioaccumulation of metals in the amphipod *Gammarus zaddachi* (Sexton 1912) from the River Hunte (Germany) and its relationship to the permeable body surface area. *Hydrobiologia* 515(1-3):11B28.
- Weltje, L. (1998) Mixture toxicity and tissue interactions of Cd, Cu, Pb and Zn in earthworms (*Oligochaeta*) in laboratory and field studies: a critical evaluation of the data. *Chemosphere* 36:2643B2660.
- Westall, JC; Zachary, JL; Morel, FMM. (1976) MINEQL, a computer program for the calculation of chemical equilibrium composition of aqueous systems. Ralph M. Parson Laboratory for Water Resources and Environ. Eng., Dept. of Civil Eng., M.I.T., Cambridge, MA. Tech. Note 18, 1976.
- Wester, RC; Maibach, HI; Sedik, L; Melendres, J; Dizio, S; Wade, M. (1992) In vitro percutaneous absorption of cadmium from water and soil into human skin. *Fundam Appl Toxicol* 19(1):1B5.
- Weston, DP; Maruya, KA. (2002) Predicting bioavailability and bioaccumulation with in vitro digestive fluid extraction. *Environ Toxicol Chem* 21(5):962B971.
- White, PD; Van Leeuwen, P; Davis, BD; Maddaloni, M; Hogan, KA; Marcus, AH; Elias, RW. (1998) The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. *Environ Health Perspect* 106(6):1513B1530.
- WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (1998) Copper. Environmental health criteria document no. 200. Geneva, Switzerland.
- WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2002) Principles and methods for the assessment of risk from essential trace elements. Environmental health criteria document no. 228. Geneva, Switzerland.

- Wilkes, CR. (1998) Case study. In: Olin, S., ed. Lead. Boca Raton, FL: CRC Press, LLC.; pp. 183B224.
- Willemson, A; Vaal, MA; De Zwart, D. (1995) Microtests as tools for environmental monitoring. NIPH and Env. Plan. (RIVM) The Netherlands; Report #9, 607042005; 39 pp.
- Wu, L; Chen, J; Tanji, KK; Bañuelos, GS. (1995) Distribution and biomagnification of selenium in a restored upland grassland contaminated by selenium from agricultural drain water. Environ Toxicol Chem 4:733B742.
- Xu, GB; Yu, CP. (1986) Effects of age deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349B357.
- Xu, J; Thornton, I. (1985) Arsenic in garden soils and vegetable crops in Cornwall, England: implications for human health. Environ Geochem Health 7:131B133.
- Yanez, L; Batres, L; Carrizales, L; Santoyo, M; Escalante, V; Diaz-Barriga, F. (1994) Toxicological assessment of azarcon, a lead salt used as a folk remedy in Mexico. I. Oral toxicity in rats. J Ethnopharmacol 41(1-2):91-7.
- Young, LB; Harvey, HH. (1991) Metal concentrations in chironomids in relation to the geochemical characteristics of surficial sediments. Arch Environ Contam Toxicol 21:202B211.
- Zartarian, VG; Ozkaynak, H; Burke, JM; Zufall, MJ; Rigas, ML; Furtaw, EJ, Jr. (2000) A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and nondietary ingestion. Environ Health Perspect 108(6):505B514.
- Zuurbier, M; Van den Hazel, P. (eds) (2005) PINCHE project: Final report WP4 risk and health impact assessment. Public Health Services. Gelderland Midden, Arnhem, The Netherlands. Available online at: http://www.pinche.hvdgm.nl/resource/pdf/documents/final/PINCHE_WP4_final_211205.pdf.

APPENDIX A: FRAMEWORK FOR METALS RISK ASSESSMENT CONTRIBUTORS AND REVIEWERS

CONTRIBUTORS AND REVIEWERS

Environmental Chemistry:

Kim Anderson, Oregon State University, Corvallis, OR
Rufus Chaney, U.S. Department of Agriculture, Beltsville, MD
Paul Chrostowski, CPF Associates, Inc., Takoma Park, MD
Miriam L. Diamond, University of Toronto, Toronto, ON, Canada
Donald Langmuir, Hydrochem Systems Corp., Colorado School of Mines, Golden, CO
Deborah Luecken, U.S. EPA, Office of Research and Development, National Exposure Research Laboratory, Research Triangle Park, NC
Michael Newman, College of William and Mary, Gloucester Point, VA
Bernard Vigneault, CANMET Mining & Mineral Sciences Laboratories/Natural Resources, Ottawa, ON, Canada

Bioavailability and Bioaccumulation:

Michael Beringer, U.S. EPA, Region VII, Kansas City, KS
John Drexler, University of Colorado, Boulder, CO
Nicholas Fisher, State University of New York, Stony Brook, NY
Gerry Henningsen, H&H Scientific Services, Centennial, CO
Roman Lanno, Ohio State University, Columbus, OH
Jim McGeer, Natural Resources Canada, Ottawa, ON, Canada

Exposure:

Gary Diamond, Syracuse Research Corp., Syracuse, NY
Charles A. Menzie, Menzie-Cura & Associates, Inc., Chelmsford, MA
Jacqueline Moya, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC
Michael Newman, The College of William and Mary, Gloucester Point, VA
Jerome Nriagu, University of Michigan, Ann Arbor, MI

Human Health Effects:

Ed Bender, U.S. EPA, Office of Research and Development, Office of Science Policy, Washington, DC (Retired)
Michael Beringer, U.S. EPA, Region VII, Kansas City, KS
Harlal Choudhury, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH
Dominic Di Toro, University of Delaware, Newark, DE
Mari Hirtzel Golub, University of California, Davis, CA
Robert Goyer, University of Western Ontario, National Research Council Board Member/Chair
Mike Hughes, U.S. EPA, Office of Research and Development, National Health and Ecological Effects Research Laboratory, Washington, DC
Richard Hertzberg, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Atlanta, GA (Retired)
Elaina Kenyon, U.S. EPA, Office of Research and Development, National Health and Ecological Effects Research Laboratory, Washington, DC

Fran Kremer, U.S. EPA, Office of Research and Development, National Risk Management
Research Laboratory, Washington, DC
Deirdre Murphy, U.S. EPA, Office of Air and Radiation, Research Triangle Park, NC

Ecological Effects:

William Clements, Colorado State University, Ft. Collins, CO
Heidi Bell, U.S. EPA, Office of Water, Washington, DC
Peter Chapman, EVS Environment Consultants, N. Vancouver, BC, Canada
Dale Hoff, U.S. EPA, Region VIII, Denver, CO
Larry Kapustka, Ecological Planning and Toxicology, Inc., Corvallis, OR
Michael Newman, The College of William and Mary, Gloucester Point, VA
Paul Paquin, HydroQual, Inc., Mahwah, NJ
Cindy Roberts, U.S. EPA, Office of Water, Washington, DC
Mark Sprenger, U.S. EPA, Office of Solid Waste and Emergency Response, Washington, DC
Dan Wall, U.S. Department of the Interior, U.S. Fish and Wildlife Service, Washington, DC
Linda Ziccardi, Exponent, Boulder, CO

METALS ISSUE PAPER AUTHORS¹

Environmental Chemistry of Metals:

Donald Langmuir, Hydrochem Systems Corp., Colorado School of Mines, Golden, CO
Paul Chrostowski, CPF Associates, Inc., Takoma Park, MD
Rufus Chaney, U.S. Department of Agriculture, Beltsville, MD
Bernard Vigneault, CANMET Mining and Mineral Sciences Laboratories/Natural Resources
Canada, Ottawa, ON

Metal Exposure Assessment:

Michael Newman, The College of William and Mary/VIMS, Gloucester Point, VA
Gary Diamond, Syracuse Research Corp., Syracuse, NY
Charles A. Menzie, Menzie-Cura & Associates, Chelmsford, MA
Jerome Nriagu, University of Michigan, Ann Arbor, MI

Ecological Effects of Metals:

Lawrence Kapustka, Ecological Planning and Toxicology, Inc., Corvallis, OR
William Clements, Colorado State University, Fort Collins, CO
Linda Ziccardi, Exponent, Boulder, CO
Paul Paquin, HydroQual, Inc., Mahwah, NJ
Mark Sprenger, U.S. EPA, Edison, NJ
Daniel Wall, U.S. Fish and Wildlife Service, Denver, CO

Human Health Effects of Metals:

Robert Goyer, University of Western Ontario, ON
Mari, Golub, University of California, Davis, CA
Harlal Choudhury, U.S. EPA, Cincinnati, OH (contributor)

Michael Hughes, U.S. EPA, Research Triangle Park, NC (contributor)
Elaina Kenyon, U.S. EPA, Research Triangle Park, NC (contributor)
Marc Stifelman, U.S. EPA, Seattle, WA (contributor)

Bioavailability and Bioaccumulation of Metals:

John Drexler, University of Colorado, Boulder, CO
Nicholas Fisher, State University of New York, Stony Brook, NY
Gerry Henningsen, H&H Scientific Services, Centennial, CO
Roman Lanno, Ohio State University, Columbus, OH
Jim McGeer, Natural Resources Canada, Ottawa, ON
Keith Sappington, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC
Michael Beringer, U.S. EPA, Region VII, Kansas City, KS (contributor)

PEER CONSULTATION WORKSHOP PARTICIPANTS**Breakout Group 1 (Overall Framework):**

Pat Doyle, Environment Canada, Ottawa, ON (breakout group lead)
Charles A. Menzie, Menzie-Cura & Associates, Chelmsford, MA (Workshop Chairman)
Bruce K. Hope, Oregon Department of Environmental Quality, Portland, OR

Breakout Group 2 (Environmental Chemistry):

Rufus Chaney, U.S. Department of Agriculture, Beltsville, MD (breakout group lead)
Donald Langmuir, Hydrochem Systems Corp., Colorado School of Mines, Golden, CO
Mark Barnett, Department of Civil Engineering, Auburn University, AL
Roman Lanno, Ohio State University, Columbus, OH
Jim Ryan, U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory, Cincinnati, OH

Breakout Group 3 (Terrestrial Exposure/Effects):

John Drexler, University of Colorado, Boulder, CO (breakout group lead)
Lawrence Kapustka, Ecological Planning and Toxicology, Inc., Corvallis, OR
Bradley Sample, CH2M Hill, Sacramento, CA
Beverly Hale, University of Guelph, Guelph, ON

Breakout Group 4 (Aquatic Exposure/Effects):

Keith Sappington, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC (breakout group lead)
David Mount, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Laboratory, Duluth, MN
Jim McGeer, Natural Resources Canada, Ottawa, ON
Steve Klaine, Clemson University, Clemson, SC
Paul Paquin, HydroQual, Inc., Mahwah, NJ
Anne Smith-Reiser, Analytical Services Inc., Jessup, MD

Breakout Group 5 (Human Exposure/Health Effects):

Steve Devito, U.S. EPA, Office of Environmental Information, Washington, DC (breakout group lead)
Mari Golub, University of California, Davis, CA
Herman Gibb, Sciences International, Alexandria, VA
Rosalind A. Schoof, Integral Consulting, Inc., Mercer Island, WA
Deirdre Murphy, U.S. EPA, Office of Research and Development, Office of Radiation, Office of Air Quality Planning and Standards, Research Triangle Park, NC

Alexander McBride, U.S. EPA, Office of Solid Waste and Emergency Response, Washington,
DC

Margaret MacDonell, U.S. Department of Energy, Argonne National Laboratory, Argonne, IL

Bob Jones, U.S. EPA, Office of Prevention, Pesticides, and Toxic Substances, Washington, DC

Richard Troast, U.S. EPA, Office of Solid Waste and Emergency Response, Washington, DC

¹ Information from the metals issue papers was used in the development of this framework



PRESORTED STANDARD
POSTAGE & FEES PAID
EPA
PERMIT NO. G-35

Office of Research and Development (8101R)
Washington, DC 20460

Official Business
Penalty for Private Use
\$300