DRAFT
DO NOT CITE OR QUOTE

EPA/630/P-04/068B
November 2004
Peer Review Draft

Framework for
Inorganic Metals Risk Assessment

NOTICE
THIS DOCUMENT IS A PRELIMINARY DRAFT. THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF PEER REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

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

DISCLAIMER

This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

LIST OF TABLES vi
LIST OF FIGURES viii
LIST OF ABBREVIATIONS AND ACRONYMS ix
PREFACE xv
AUTHORS, CONTRIBUTORS, AND REVIEWERS xviii
EXECUTIVE SUMMARY xxv

1. INTRODUCTION 1-1
   1.1. PURPOSE AND AUDIENCE 1-1
   1.2. METALS FRAMEWORK SCOPE 1-2
   1.3. RISK ASSESSMENT FRAMEWORK 1-3
   1.4. METALS ASSESSMENT CONTEXT 1-5
      1.4.1. National Ranking and Categorization 1-5
      1.4.2. National-Level Assessments 1-7
      1.4.3. Site-Specific Assessments 1-8
   1.5. ORGANIZATION OF METALS FRAMEWORK 1-9

2. PROBLEM FORMULATION AND METALS PRINCIPLES 2-1
   2.1. PRINCIPLES OF METALS RISK ASSESSMENT 2-2
      2.1.1. Environmental Background Concentrations 2-2
      2.1.2. Essentiality 2-3
      2.1.3. Environmental Chemistry 2-4
      2.1.4. Bioavailability 2-6
      2.1.5 Bioaccumulation and Bioconcentration 2-9
      2.1.6 Acclimation, Adaptation, and Tolerance 2-10
      2.1.7. Toxicity Testing 2-10
      2.1.8. Mixtures 2-11
   2.2. METALS CONCEPTUAL MODEL 2-12
   2.3. NEXT STEPS 2-17

3. METALS RISK ASSESSMENT RECOMMENDATIONS 3-1
   3.1. HUMAN HEALTH RISK ASSESSMENT RECOMMENDATIONS 3-1
      3.1.1. Fate and Transport 3-2
      3.1.2. Exposure Assessment 3-2
      3.1.3. Effects Analysis 3-7
   3.2. METALS RISK ASSESSMENT RECOMMENDATIONS FOR AQUATIC ENVIRONMENT 3-10
      3.2.1. Fate and Transport 3-10
      3.2.2. Water Column Exposure, Bioavailability, and Effects 3-12
      3.2.3. Background 3-15
      3.2.4. Bioaccumulation 3-16

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

CONTENTS (continued)

3.2.5. Trophic Transfer, Biomagnification, and Dietary Toxicity 3-18
3.2.6. Sediment Exposure and Effects 3-20
3.2.7. Metals Mixtures 3-21
3.3. METALS RISK ASSESSMENT RECOMMENDATIONS FOR TERRESTRIAL ECOSYSTEMS 3-21
3.3.1. Fate and Transport. 3-22
3.3.2. Exposure Assessment 3-25
3.3.3. Toxicity Assessment 3-34

4. METAL-SPECIFIC TOPICS AND METHODS 4-1
4.1. ENVIRONMENTAL CHEMISTRY 4-1
4.1.1. Introduction and Terminology 4-1
4.1.2. Hard and Soft Acids and Bases: The Stability of Complexes 4-2
4.1.3. Aquatic Chemistry 4-4
4.1.4. Ground Water and Metal Mobility 4-10
4.1.5. Sediment Chemistry 4-17
4.1.6. Soil Chemistry 4-23
4.1.7. Atmospheric Behavior/Chemistry 4-32
4.1.8. Metal Speciation Techniques 4- 34
4.1.9. Organo-Metals/Metalloids Transformation Processes 4-36
4.2. HUMAN HEALTH EXPOSURE PATHWAY ANALYSIS 4-44
4.2.1. Introduction 4-44
4.2.2. Human Exposure 4-44
4.2.3. Physiological Routes of Entry 4-52
4.2.4. Integrated Exposure Approaches 4-52
4.2.5. Toxicokinetics and Toxicodynamics 4-62
4.2.6. Pharmacokinetic/Pharmacodynamic Modeling of Metals 4-67
4.3. HUMAN HEALTH EFFECTS 4-71
4.3.1. Introduction 4-71
4.3.2. Essentiality Versus Toxicity 4-71
4.3.3. RDAs and RfDs/RfCs 4-73
4.3.4. Biology Relevant to Toxic and Essential Properties of Metals 4-74
4.3.5. Toxicity 4-76
4.3.6. Metals Mixtures 4-77
4.3.7. Variations in Susceptibility 4-82
4.4. ECOLOGICAL EXPOSURE PATHWAY ANALYSIS 4-88
4.4.1. Aquatic and Terrestrial Transport Pathways for Metals 4-89
4.4.2. Routes of Exposure to Aquatic and Terrestrial Species 4-103
4.4.3. Food Chain Modeling for Wildlife 4-121
4.5. CHARACTERIZATION OF ECOLOGICAL EFFECTS 4-126
4.5.1. Essentiality 4-126

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

CONTENTS (continued)

4.5.2. Acclimation and Adaptation 4-129
4.5.3. Metals Mixtures 4-135
4.5.4. Background 4-140
4.5.5. Indirect Effects of Metals 4-144
4.5.6. Bioavailability in Terrestrial Systems 4-147
4.5.7. Bioavailability in Aquatic Systems 4-152
4.5.8. Bioaccumulation and Bioconcentration in Aquatic Organisms 4-160
4.5.9. Bioaccumulation in Terrestrial Organisms 4-170
4.5.10. Sediment Toxicity: Equilibrium Partitioning Approach for Metals 4-174
4.5.11. Soil Toxicity 4-181
4.5.12. Food Chain (Wildlife) Toxicity 4-184

5. METALS RESEARCH NEEDS 5-1
5.1. U.S. EPA RESEARCH 5-1
5.2. EXTERNAL RESEARCH 5-2
5.3. SPECIFIC RECOMMENDATIONS 5-3
5.3.1. Environmental Chemistry 5-3
5.3.2. Bioaccumulation and Bioavailability 5-4
5.3.3. Exposure 5-5
5.3.4. Human Health Effects 5-6
5.3.5. Characterization of Ecological Effects 5-7
5.3.6. Unit World Model for Metals 5-8

GLOSSARY 6-1

REFERENCES 7-1

APPENDIX A-1

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF TABLES

Table 2-1. Classification of metals based on characteristics of health effects 2-4

Table 2-2. Factors that primarily control metal sorption to soils, aquifers, and sediments . . 2-6

Table 4-1. Hard and soft acids (metal cations) and bases (ligands) 4-3

Table 4-2. Important properties of trace metals as they occur in natural waters and mineral systems: oxidation states, redox sensitivity, tendency to form sulfides at low Eh, dominant chemical species of metals in soils and natural waters not considering most (especially weak) metal complexes 4-9

Table 4-3. Comparison of model predictions and measured values of percent metals associated with the suspended particulate fraction of mine drainage waters from selected sites 4-13

Table 4-4. Partition coefficients as a function of pH for several important elements of potential concern 4-16

Table 4-5. Time to achieve 95% of steady-state metal concentration in soil and total soil metal concentrations after 100 years and at steady state 4-28

Table 4-6. Some stable organometallic compounds 4-37

Table 4-7. Metals/metalloids involved in methylation processes 4-37

Table 4-8. General trends of environmental factors affecting rates of methylation/demethylation 4-40

Table 4-9. Metal speciation techniques for solids and their associated pore waters 4-43

Table 4-10. Metal (versus organic) compound properties affecting absorption, distribution, metabolism, and elimination 4-63

Table 4-11. Kinetic factors to consider when evaluating the use of PBPK models or other dosimetric adjustments in the risk assessment process for metals in humans . . 4-69

Table 4-12. Metals classified by their known essentiality 4-71

Table 4-13. List of fate and transport models 4-95

Table 4-14. Metals classified by their known essentiality 4-128

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF TABLES (continued)

Table 4-15. Maximum tolerable levels of dietary minerals for domestic livestock in comparison with levels in forages 4-132

Table 4-16. Examples of indirect effects of metal toxicity 4-145

Table 4-17. Qualitative bioavailability of metal cations in natural soils to plants and soil invertebrates 4-150

Table 4-18. Qualitative bioavailability of metal anions in natural soils to plants and soil invertebrates 4-150

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF FIGURES

Figure 1-1. Risk assessment/risk management process for metals 1-4

Figure 2-1. Health effect curves for (a) essential elements and (b) nonessential metals 2-5

Figure 2-2. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems 2-7

Figure 2-3. Generic conceptual model for metals risk assessments 2-14

Figure 4-1. Approximate positions of some natural environment in terms of Eh and pH . . . 4-6

Figure 4-2. Sequence of microbially mediated oxidation-reduction reactions 4-7

Figure 4-3. Adsorption of various metal cations and oxyanions, each at 5×10^{-7} M, by ferrihydrite ($\Sigma Fe[III] = 10^{-3}$ M) as a function of pH at ionic strength of 0.1 mol/kg 4-26

Figure 4-4. Dose-response curves for essential elements 4-72

Figure 4-5. A generalized framework for chemical fate and transport in aquatic systems . . 4-92

Figure 4-6. Conceptual model for direct and indirect exposure of ecological receptors to metals in soil zones 4-115

Figure 4-7. Relative contribution of incidental soil ingestion to oral dose for wildlife at different soil ingestion rates and bioaccumulation factors, and a bioavailability of 100% 4-120

Figure 4-8. Wildlife Oral Exposure Model 4-123

Figure 4-9. Linkages between dietary toxicity threshold, bioaccumulation in prey organisms and waterborne exposure 4-169

Figure 5-1. Schematic representation of the Unit World Model for metals 5-10

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF ABBREVIATIONS AND ACRONYMS

1CFOK	One-Compartment, First-Order Kinetics Model
ABA	Absolute bioavailability
aBLM	Aquatic Biotic Ligand Model
ACF	Accumulation factor
AEC	Anion exchange capacity
AESOP	Advanced Ecological Systems Operating Program
AI	Adequate intake
ALA	Aminolevulinic acid
ALM	Adult lead methodology
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
AUC	Area under the curve
AVS	Acid-volatile sulfide
AWQC	Ambient Water Quality Criteria
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BF	Bioaccessible fraction
BLM	Biotic Ligand Model
BMD	Benchmark dose
BSAF	Biota/sediment accumulation factor
CAA	Clean Air Act
CATM	Center for Air Toxic Metals
CBR	Critical body residue
CCA	Chromated copper arsenate
CCC	Criterion continuous concentration
CEC	Cation exchange capacity
CHESS	Chemical Equilibria in Soils and Solutions
CHMTRNS	Chemical Transport model
CHNTRN	Channel Transport model
CMAQ	Community Multi-scale Air Quality model
CMC	Criterion maximum concentration

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

1	CSF	Cancer slope factor
2	CTAP	Chemical Transport and Analysis Program
3	CWA	Clean Water Act
4	DELFT3D	Delft 3-Dimensional model
5	DEPM	Dietary Exposure Potential Model
6	DHHS	U.S. Department of Health and Human Services
7	DJOC	Donald J. O'Connor model
8	DL	Diffuse Layer model
9	DOC	Dissolved organic carbon
10	DOM	Dissolved organic matter
11	DYNTOX	Dynamic Toxics model
12	EC	Effect concentration
13	ECOFRAM	Ecological Committee on FIFRA Risk Assessment Methods
14	ECOM	Estuary, Coastal, Ocean Model
15	ECOMSED	Estuary, Coastal, Ocean Model (ECOM) updated for sediment transport
16	EcoSSL	Ecological soil screening level
17	EERC	Energy and Environmental Research Center (University of North Dakota)
18	Eh	Redox (reduction-oxidation) potential
19	EPMA-SEM	Electron probe microanalysis-scanning electron microscopy
20	EqP	Equilibrium partitioning
21	ESB	Equilibrium partitioning sediment benchmark
22	EU	European Union
23	EUSES	European Union System for the Evaluation of Substances model
24	EUTRO	Water Quality Analysis Simulation Program (WASP) for Eutrophication
25	EXAMS	Exposure Analysis Modeling System
26	f_{OC}	Fraction of organic carbon (mass, for sediment)
27	FAV	Final acute value
28	FCV	Final chronic value
29	FDA	Food and Drug Administration
30	FETRA	Sediment/Radionuclide Transport Model
31	FIAM	Free Ion Activity Model
32	FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

1	FNB	Food and Nutrition Board (NAS)
2	GI	Gastrointestinal tract
3	GM	General Motors III model
4	GMAV	Genus mean acute value
5	GSIM	Gill Surface Interaction Model
6	GTLM	Generalized Two-Layer Model
7	HFO	Hydrous ferric oxide
8	HLA	Human leukocyte antigens
9	HOC	Hydrophobic organic compound
10	HSAB	Hard and soft acid and base
11	HSP	Hydrologic Simulation Program *(Fortran program also referenced as HSPF)*
12	HSPF	Hydrologic Simulation Fortran Program
13	HSRC	Hazardous Substance Research Center
14	HST3D	3-Dimensional Flow, Heat and Solute Transport model
15	IBM	Ion Balance Model
16	ICP-MS	Inductively coupled plasma-mass spectrometry
17	IEUBK	Integrated Exposure Uptake Biokinetic model
18	IRIS	Integrated Risk Information System
19	IWBU	Interstitial Water Benchmark Unit
20	K_d	Partition distribution coefficient
21	K_{ow}	Octanol-water partition coefficient
22	LC_x	Lethal concentration (for x percent of the study population)
23	LOAEL	Lowest-observed-adverse-effect level
24	MAP	Metals Action Plan
25	M:BL	Metal-Biotic Ligand model
26	MCL	Maximum contaminant level
27	META4	Metal Exposure and Transformation Assessment model
28	MEXAMS	Metals Exposure Analysis Modeling Systems
29	MITE-RN	Metals in the Environment Research Network
30	MNA	Monitored natural attenuation
31	MT	Metallothionein
32	MW	Molecular weight

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

1	NAS	National Academy of Sciences
2	NAS/IOM	National Academy of Sciences/Institute of Medicine
3	NASQAN	National Stream Quality Accounting Network
4	NIEHS	National Institute of Environmental Health Sciences
5	NOAEL	No-observed-adverse-effect level
6	NOM	Natural organic matter
7	NRC	National Research Council
8	OAR	Office of Air and Radiation (EPA)
9	OECD	Organization for Economic Cooperation and Development
10	OM	Organic matter
11	OP	Organophosphorous
12	OPIDN	Organophosphate-induced delayed neurotoxicity
13	OPP	Office of Pesticide Programs (EPA)
14	ORD	Office of Research and Development (EPA)
15	OST	Office of Water, Office of Science and Technology (EPA)
16	OSWER	Office of Solid Waste and Emergency Response (EPA)
17	Pawtoxic	Pawtuxent Toxic model
18	PbL	Blood lead
19	PBPD	Physiologically based pharmacodynamic
20	PBPK	Physiologically based pharmacokinetic
21	PBT	Persistent bioaccumulative toxic
22	PBTK	Physiologically based toxicokinetic
23	PDM	Probabilistic Dilution Model
24	pE	Negative log of electron activity
25	PEC	Predicted environmental concentration
26	PNEC	Predicted no-effect concentration
27	PICT	Pollution-induced community tolerance
28	PIXE	Particle induced x-ray emission (also μPIXE)
29	PM	Particulate matter
30	POC	Particulate organic carbon
31	QICAR	Quantitative ion character-activity relationship
32	QSAR	Quantitative structure-activity relationship

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

QWASI	Quantitative Water Air Sediment Interaction model
RAF	Relative absorption factor
RAGS	Risk Assessment Guidance for Superfund
RBA	Relative bioavailability
RCATOX	Row-Column Advanced ecological systems operating program for Toxics model
RCRA	Resource Conservation and Recovery Act
RDA	Recommended dietary allowance
RfC	Reference concentration
RfD	Reference dose
RIVEQLII	River Quality II model
RIVRISK	River Risk model
RTC	Report to Congress
SAB	Science Advisory Board
SCAMP	Surface Chemistry Assemblage Model for Particles
SEM	Simultaneously extracted metals
SERATRA	Sediment Radionuclide Transport model
SHEDS	Stochastic Human Exposure and Dose Simulation model
SIMS	Secondary ion mass spectrometry
SLSA	Simplified Lake and Stream Analysis model
SMAV	Species mean acute value
SPC	Science Policy Council (EPA)
SPM	Suspended particulate matter
SMPTOX	Simplified Method-Program Variable-Complexity Stream Toxics
SPQ	Hydrologic Simulation Program-FORTRAN model
SQG	Sediment quality guideline
SRWG	Science and Research Working Group (SRWG) of the Non-Ferrous Metals Consultative Forum on Sustainable Development
SSD	Species sensitivity distribution
STATSGO	State Soil Geographic Database
STORET	Storage and Retrieval data system
tBLM	Terrestrial Biotic Ligand Model

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

TD	Toxicodynamic
TEF	Toxicity equivalence factor
TIE	Toxicity identification evaluation
TMDL	Total maximum daily load
TRANSPEC	Transport and Speciation model
TRIM	Total Risk Integrated Methodology model
TRIM.FaTE	Total Risk Integrated Methodology Fate, Transport, and Ecological Exposure model
TRV	Toxicity reference value
TSCA	Toxic Substances Control Act
TTD	Target-organ toxicity dose
TTM	Total toxicity of mixture
TU	Toxic unit
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
VOC	Volatile organic compound
WASP	Water Quality Analysis Simulation Program
WASTOX	Water Quality Analysis Simulation of Toxics
WER	Water-effect ratio
WHAM	Windermere Humic Aqueous Model
WHO	World Health Organization
WHO/IPCS	World Health Organization/International Programme on Chemical Safety
WOE	Weight of evidence
WQAM	Water Quality Assessment Methodology model
WQC	Water quality criterion
WQG	Water quality guideline
XAS	X-ray absorption spectroscopy
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

PREFACE

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

EPA's Science Policy Council recognizes that metals present unique risk assessment issues and tasked an Agency workgroup, under the auspices of EPA's Risk Assessment Forum, with 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 metal-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 MAP and continuing with framework development and review. Workshops and peer-review activities were conducted at multiple intervals during framework production to ensure current and accurate science that supported 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. Additional details on these activities are provided below.

MAP Stakeholder Input. In February 2002, a meeting was convened to gather stakeholder input to help EPA formulate the plan for developing this framework. EPA solicited input on organization and content and received comments that were adopted to the extent practicable. 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Science Advisory Board Review. In September 2002, EPA's SAB reviewed the MAP and provided comments. Some of the panel's recommendations are summarized below, and all are available in full at http://www.epa.gov/sab/pdf/ecl03001.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 some 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. Issue papers were developed to discuss key scientific topics pertaining to inorganic metals. The issue paper authors were asked to expand on these topics, with focus on decison-making applications, framework-specific uses, and research needs. The papers are available at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119. The topics and primary questions addressed by the papers include the following:

- **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, dietary salts, and others?

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Peer Consultation Workshop. A draft framework was completed in July 2004, and a peer consultation workshop was held on July 27–28 to seek input from scientists expert in the field of metals risk assessment. Scientists participating in the workshop were from academia; industry, state, federal, and Canadian agencies; and various Offices within EPA. Stakeholder comments were also received for consideration. Based on comments received at the workshop, the Agency contracted with a few workshop participants to expand on several gaps and issues identified in the human health and environmental chemistry discussions. The document was revised, and the revised report was made available for inter-Agency review.

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

SAB Review and Public Comment. Pending.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CO-CHAIRS

Anne Fairbrother, U.S. EPA, Office of Research and Development, National Health and Environmental Effects Laboratory, Corvallis, OR

Randy Wentsel, U.S. EPA, Office of Water, Washington, DC

STEERING COMMITTEE

Marilyn Brower, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Risk Assessment Forum, Washington, DC

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

Pamela Noyes, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Risk Assessment Forum, Washington, DC

Keith Sappington, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC

William Wood, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Risk Assessment Forum, Washington, DC

CONTRIBUTORS

Environmental Chemistry:

Kim Anderson, Oregon State University, Corvallis, OR

Rufus Chaney, U.S. Department of Agriculture, Beltsville, MD[1]

Paul Chrostowski, CPF Associates, Inc., Takoma Park, MD[1]

Miriam L. Diamond, University of Toronto, Toronto, ON, Canada

Robert Ford, U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory, Ada, OK

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Donald Langmuir, Hydrochem Systems Corp., Colorado School of Mines, Golden, CO[1]

Deborah Luecken, U.S. EPA, Office of Research and Development, National Exposure Research Laboratory, Research Triangle Park, NC

Michael Newman, The College of William and Mary, Gloucester Point, VA

Robert Puls, U.S. EPA, Office of Research and Development, National Risk Management Research Laboratory, Ada, OK

Bernard Vigneault, CANMET Mining & Mineral Sciences Laboratories/Natural Resources, Ottawa, ON, Canada[1]

Bioavailability and Bioaccumulation:

Michael Beringer, U.S. EPA, Region VII, Kansas City, KS

John Drexler, University of Colorado, Boulder, CO[1]

Nicholas Fisher, State University of New York, Stony Brook, NY[1]

Gerry Henningsen, H&H Scientific Services, Centennial, CO[1]

Roman Lanno, Ohio State University, Columbus, OH[1]

Jim McGeer, Natural Resources Canada, Ottawa, ON, Canada[1]

Keith Sappington, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC[1]

Exposure:

Gary Diamond, Syracuse Research Corp., Syracuse, NY[1]

Charlie Menzie, Menzie-Cura & Associates, Inc., Chelmsford, MA[1]

Jacqueline Moya, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Washington, DC[1]

Michael Newman, The College of William and Mary, Gloucester Point, VA[1]

Jerome Nriagu, University of Michigan, Ann Arbor, MI[1]

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Human Health Effects:

Ed Bender, U.S. EPA, Office of Research and Development, Office of Science Policy, Washington, DC

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[1]

Dominic Di Toro, University of Delaware, Newark, DE

Mari Hirtzel Golub, University of California, Davis, CA[1]

Robert Goyer, University of Western Ontario, National Research Council Board Member/Chair[1]

Mike Hughes, U.S. EPA, Office of Research and Development, National Health and Ecological Effects Research Laboratory, Washington, DC[1]

Richard Hertzberg, U.S. EPA, Office of Research and Development, National Center for Environmental Assessment, Atlanta, GA

Elaina Kenyon, U.S. EPA, Office of Research and Development, National Health and Ecological Effects Research Laboratory, Washington, DC[1]

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, Research Triangle Park, NC

Mark Stifelman, U.S. EPA, Region X, Seattle, WA[1]

Ecological Effects:

William Clements, Colorado State University, Ft. Collins, CO[1]

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[1]

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Michael Newman, The College of William and Mary, Gloucester Point, VA

Paul Paquin, HydroQual, Inc., Mahwah, NJ[1]

Cindy Roberts, U.S. EPA, Office of Water, Washington, DC

Mark Sprenger, U.S. EPA, Office of Solid Waste and Emergency Response, Washington, DC[1]

Dan Wall, U.S. Department of the Interior, U.S. Fish and Wildlife Service, Washington, DC

Linda Ziccardi, Exponent, Boulder, CO[1]

METALS ISSUE PAPER AUTHORS[2]

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 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 Menzie, Menzie-Cura & Associates, Chelmsford, MA (Workshop Chairman)

Bruce K. Hope, Oregon Department of Environmental Quality, Portland, OR

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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]Scientific expert commissioned to develop paper on issues and state-of-the-art approaches in metals risk assessment.

[2] Information from the metals issue papers was used in the development of this framework.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

EXECUTIVE SUMMARY

The Framework for Inorganic Metals Risk Assessment is a science-based document that addresses the special attributes and behaviors of metals and metal compounds when assessing their human health and ecological risks. The document describes basic principles to be considered in assessing risks posed by metals and presents a consistent approach for use across the Agency when conducting these assessments. Although the audience for the framework is primarily intended to be Agency risk assessors, it will also communicate principles, tools, and recommendations for metal risk assessment to stakeholders and the public. The Agency developed this framework document to supplement previous guidance for use in site-specific risk assessments, criteria derivation, ranking or categorization, and other similar Agency activities related to metals.

One of the purposes of this document is to present key principles that contain specific issues which differentiate inorganic metals from other chemicals when assessing their risk to human health and the environment. While we recognize that organic compounds, for example, undergo bioaccumulation, there are unique properties, issues, and processes within these principles that assessors need to consider when evaluating metal compounds. For example, the latest scientific data on bioaccumulation do not currently support the use of bioconcentration factor (BCF) and bioaccumulation factor (BAF) data when applied as generic threshold criteria for the hazard potential of inorganic metals (e.g., for classification as a "PBT" chemical). These principles should be addressed and incorporated into metals risk assessment to the extent practicable. They include the following:

• Environmental background concentrations • Essentiality • Environmental chemistry • Bioavailability	• Accumulation/bioaccumulation and bioconcentration • Acclimation, adaptation, and tolerance • Toxicity testing • Mixtures

This document discusses, in Section 2, why these principles are important in ecological and human health risk assessments and presents conceptual models on metal-specific attributes and bioavailability. In Section 3, the framework provides assessors with recommendations and method applications, and supports these recommendations with technical discussions, in Section 4, on metal-specific topics, including environmental chemistry, human health exposure pathway and effects analysis, and ecological exposure pathway and effects analysis. Section 5 presents

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

research needs to improve the science supporting the assessment of metals and metal compounds. This framework document will not be a prescriptive guide on how any particular type of assessment should be conducted within a U.S. EPA program office. Rather, it is intended to provide recommendations and foster the consistent application of methods and data to metals risk assessment in consideration of the unique properties of metals.

While this document discusses scientific issues and makes recommendations about scientific approaches, this framework does not address the science policy questions and issues which are raised. Rather, it is intended to make recommendations and foster the consistent application of methods and data to metals risk assessment in consideration of the unique properties of metals. Consistent with these recommendations, the Agency will be analyzing the science policy implications and developing appropriate policy approaches which 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

1. INTRODUCTION

Metals and metal compounds have unique characteristics that should be considered when assessing their risks. Some of these characteristics are typically not considered when assessing the risks of organic substances. For example, although 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 metal and some inorganic 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 are essential elements at low levels but toxic at higher levels (e.g., copper, selenium, and zinc), whereas others have no known biological functions (e.g., lead, arsenic, and mercury). Because metals are naturally occurring, many organisms have evolved mechanisms to regulate accumulations, especially those of essential metals. Because the majority of compounds assessed by the U.S. 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.

1.1. PURPOSE AND AUDIENCE

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

The inorganic metals risk assessment framework describes basic principles to be considered in assessing risks posed by metals and presents a consistent approach for use across the Agency when conducting these assessments. Although the primary audience will be Agency risk assessors, the framework will also communicate principles, tools, and recommendations for metals risk assessment to stakeholders and the public. In addition, the framework relies heavily on issue papers developed, under EPA commission, on key scientific topics pertaining to inorganic metals. The papers are available on EPA's website at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119.

The metals framework is intended for guidance only. It does not establish any substantive "rules" under the Administrative Procedure Act or any other law and will have no

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

binding effect on EPA or any regulated entity. Rather, it represents a nonbinding statement of policy. EPA believes that the metals framework provides a sound, up-to-date presentation of principles, tools, and recommendations for assessing the risk posed by metals and serves to enhance the application of the best available science in Agency risk assessments. However, EPA may conduct metals risk assessments using approaches and tools 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. The science surrounding metals risk assessment continues to be intensively studied and thus is rapidly evolving. Specific principles, tools, or recommendations presented in the framework may become outdated or may otherwise require modification to reflect the best available science. Application of this framework in future metals risk assessments will be based on 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 metals risk assessment framework is a science-based document that focuses on the special attributes and behaviors of metals and metal compounds affecting human health and ecological risk assessments. It does not set forth a step-by-step process to assess the risk of metals to human health or the environment but, rather, focuses on principles, tools, and methods coupled with recommendations to guide assessors in addressing the unique properties of inorganic metals. It supplements existing guidance and does not cover elements of the risk assessment process that are not unique to metals because these are adequately addressed in other Agency guidelines and strategies (e.g., U.S. EPA, 2003a, 2000a, 1998a).

The Agency regulates metals and their inorganic and organometallic compounds because they have the potential to harm human health and the environment. The Agency's Science Advisory Board 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

Metals and Metalloids of 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	

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

organic substances and inorganic metal compounds, the properties of both the organic moieties of these compounds and their inorganic components would need to be addressed. Frameworks and associated guidance documents for assessing properties of organic compounds have already been developed by EPA and do not need to be discussed further here. Therefore, this document addresses only those assessment issues associated with inorganic metal compounds. The framework does discuss natural transformation pathways that form organometallic compounds and refers the reader to appropriate Agency documentation or research efforts related to relevant risk assessment issues.

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

1.3. RISK ASSESSMENT FRAMEWORK

Risk assessment provides a qualitative and quantitative comparison of the relationship between environmental exposures and effects in exposed individuals and other organisms. In 1983, the National Research Council described four primary steps in the process of risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. EPA has developed a similar framework for ecological risk assessment and included a problem formulation step (U.S. EPA, 1998a). This framework document provides recommendations, including applications and limitations of currently available tools and methods, for conducting metals risk assessment. These recommendations are designed to be incorporated into current principles and elements of human health and ecological risk assessment guidance developed by the U.S. EPA (e.g., U.S. EPA, 2003a, 2000a, 1998a). Additional general risk assessment information is also available on EPA's website at http://cfpub.epa.gov/ncea/ and http://cfpub.epa.gov/ncea/raf/index.cfm.

Figure 1-1 broadly illustrates the overall risk assessment/risk management process, and by way of example, identifies in the problem formulation and analysis steps some metals-specific considerations. An effective risk assessment for metals will consider the unique aspects of metals, differentiating them from other substances, early and throughout the risk assessment process. These unique aspects are captured and formulated in this framework as metals concepts and principles; they are summarized in Section 2 and discussed throughout the framework. They include environmental background concentrations; essentiality; environmental chemistry; bioavailability; bioaccumulation and bioconcentration; acclimation, adaptation, and tolerance; toxicity testing; and mixtures.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

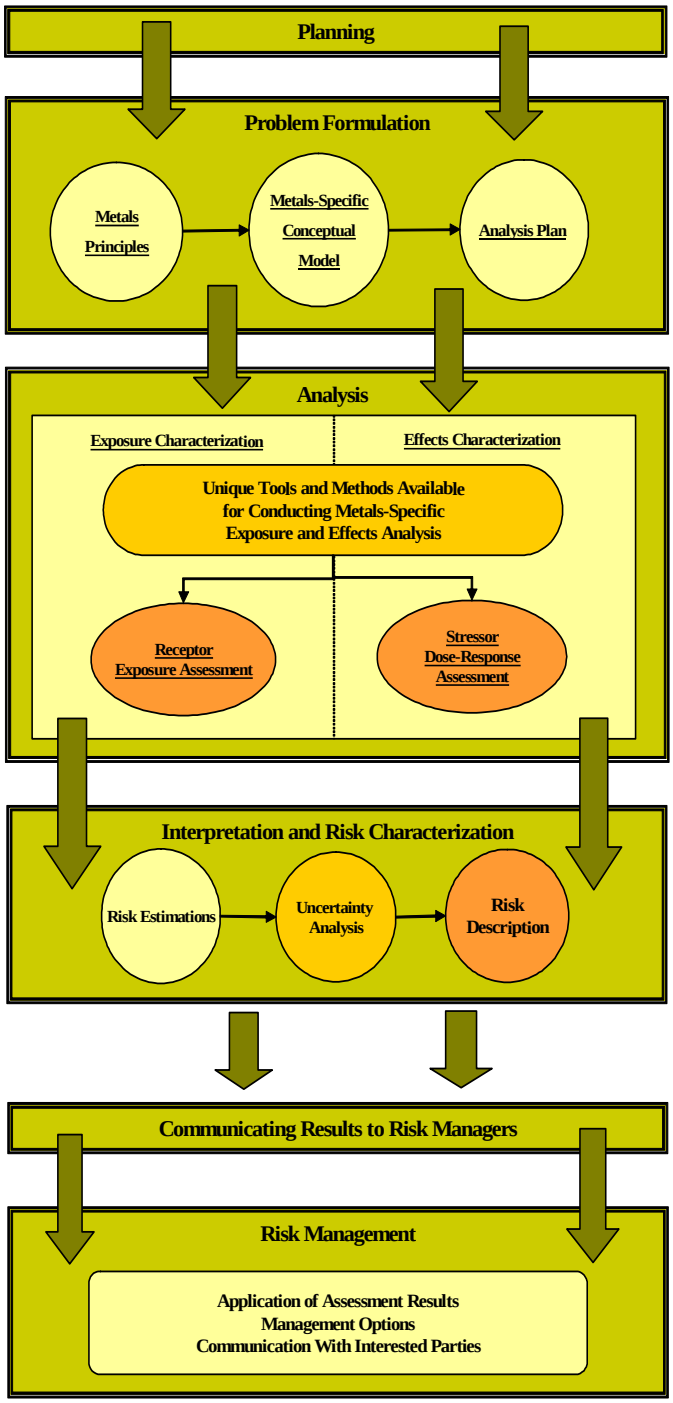

Figure 1-1. Risk assessment/risk management process for metals.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

1.4. METALS ASSESSMENT CONTEXT

The context for the risk assessment is a major factor in determining the type of analysis that is appropriate for any particular situation. To provide a context for discussion of the framework principles for metals, EPA has defined three general categories of assessments: 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 highly complex definitive assessments.

1.4.1. National Ranking and Categorization

In the first type of assessment, EPA may rank or categorize chemicals on the basis of their potential to cause risk. For many chemicals, there are significant data gaps regarding their chemistry, environmental fate, toxicity, or exposure potential, notably with regard to location-specific characteristics that directly influence these factors and make broad generalizations difficult. Nonetheless, EPA is tasked with protecting human health and the environment from the potentially harmful effects of these chemicals and thus had to develop methods to identify those most likely to pose a significant threat.

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.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Some of the ranking and categorization methods used by EPA involve identifying certain attributes of chemicals that can then be used as indicators of potential risk. Example attributes include toxicity, production volume, quantities released to the environment, persistence in the environment, mobility in the environment as indicated by volatility or solubility, and potential to accumulate in the food chain. Other methods, which may be less quantitative, rely more on a combination of expert 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 include the following:

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

Ambient Water Quality Criteria

EPA's Office of Water is charged with developing Ambient Water Quality Criteria (AWQC) to support the Clean Water Act goals of protecting and maintaining physical, chemical, and biological integrity of waters of the United States. Examples of chemical-specific criteria include those designed to protect human health, aquatic life, and wildlife. Although AWQC are typically derived at a national level, there is a long history behind the development of methods to accommodate site-specific differences in metals bioavailability. For example, since the 1980s aquatic life criteria for several cationic metals have been expressed as a function of water hardness to address the combined effect of certain cations (principally calcium and magnesium) on toxicity.

Recognizing that water hardness adjustments did not account for other important ions and ligands that can alter metals bioavailability and toxicity, EPA developed the Water Effect Ratio (WER) procedure as an empirical approach for making site-specific bioavailability adjustments to criteria (U.S. EPA, 1994a). This approach relies on comparing toxicity measurements made in site water with those made in laboratory water to derive a WER. The WER is then used to adjust the national criterion to reflect site-specific bioavailability.

More recently, the Office of Water has been developing a mechanistic-based approach for addressing metals bioavailability using the Biotic Ligand Model (BLM) (U.S. EPA, 2000b; Di Toro et al., 2001; Santore et al., 2001). This model, which is described in further detail in Section 4, 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Setting priorities for reviewing existing chemicals under TSCA.

This list of needs for ranking or categorizing chemicals is not comprehensive but does provide an indication of the kinds of 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.

1.4.2. 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, pesticide registrations). EPA also is charged with establishing controls on environmental releases based on the best available treatment technologies (e.g., maximum achievable control technology for air emissions, best available treatment technology for surface water discharges and for hazardous wastes). However, even though the standards are based on technological achievability, the Agency typically performs risk assessments in support of these regulations to help inform management decisions and for use in cost/benefit analyses.

Differing environmental conditions across the country affect the biogeochemistry of metals, making it difficult to set single-value national criteria (national standards that apply at the point of exposure, such as MCLs, are less affected by these factors). 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 of the factors that may affect potential risk, including environmental factors affecting the fate, transport, exposure potential, and toxicity of the chemicals released.

Another common approach for a national assessment or criteria derivation is to conduct a probabilistic analysis (such as a Monte Carlo analysis), wherein the variability of the key factors

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

is described by parameter distributions used as inputs to the probability analysis procedure. The result is an integrated distribution of potential risk levels. The difficulties related to conducting this kind of analysis are in developing appropriate distributions for each parameter and in ensuring that adequate attention is paid to potential correlations among key parameters. These correlations often are more complex and difficult to describe for metals than for organic compounds.

1.4.3. Site-Specific Assessments

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

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

An accurate site-specific assessment for a metal requires knowledge of the form 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 that might accumulate the metal as well as the uptake factors for whatever form(s) the metal may be in, plausible pathways and routes of exposures to the human or ecological receptors, and the effect the metal will have on target organisms in whatever form in which it reaches that organism and

Establishing Water Discharge Permit Conditions

The Clean Water Act establishes a two-tier process for setting water discharge permit conditions. First, all dischargers must meet the technology-based effluent guidelines limitations requirements. Second, if those limitations are not adequate to allow the receiving stream to achieve its designated water quality standards, then more stringent limits are developed to ensure that those standards are met.

The water quality standards are established by the states and consist of a designated use for the waterbody and a set of criteria for individual chemicals that allow that use to be achieved. EPA has published national water quality criteria values for the states to use as guidance in setting their standards.

Once the standards that include the criteria have been established and it has been determined that the effluent guidelines alone will not be sufficient to allow those criteria to be met, the state prepares a wasteload allocation for all the dischargers to that stream segment, including, where appropriate, the nonpoint source discharges. The wasteload allocation generally consists of modeling the potential impact on the stream from each discharge of the 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

its target organ/system. Although many of these same factors also affect the risk potential of organic chemicals, models for predicting fate, transport, and toxic properties are generally better defined for organic chemicals than for metals.

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

1.5. Organization of Metals Framework

The framework includes sections on metals principles and conceptual models, recommended methods for metals assessment, and metal-specific topics and methods. Section 2 begins with a discussion of metals principles and their importance in the assessment of inorganic metals. A conceptual model is presented that highlights the areas where metal-specific information is required to move through the risk assessment, criteria development, or classification/ranking process. This discussion provides additional direction to where in the document the guidance material is discussed for each issue identified. Also in Section 2, a conceptual model on bioavailability is presented (McGeer et al., 2004) along with definitions developed by authors of the issue papers.

Section 3 provides recommendations to guide risk assessors in incorporating metal-specific issues and application of tools and methods into the phases and levels of risk assessment. Discussion is included about which tools are appropriate for screening-level assessments and which information is most useful for detailed, in-depth analyses. Detailed discussion of metal-specific tools and methods occurs in Section 4, where each subsection is devoted to a particular metals issue. Specifically, Section 4 is organized as follows:

- Section 4.1. Environmental Chemistry
- Section 4.2. Human Exposure Pathway Analysis
- Section 4.3. Human Health Effects
- Section 4.4. Ecological Exposure Pathway Analysis
- Section 4.5. Characterization of Ecological Effects

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

It is important to stress that Section 4 does not precisely follow the risk assessment framework of exposure assessment and effects assessment but, rather, presents all the necessary metal-specific attributes to consider when conducting a hazard and risk assessment. This is because several of the issues are cross-cutting (e.g., environmental chemistry discussions in Section 4.1) and may have application to both exposure and effects assessments. Furthermore, because this framework addresses only the aspects of the risk or hazard assessment that are specific to metals, it does not provide a comprehensive overview of the entire process.

The document concludes with a discussion about research under way, planned, and needed to reduce uncertainty (Section 5). Although our understanding about metals issues is broad based, specific methods and data are more readily available in some areas (e.g., freshwater ecosystems) than in others (e.g., soils). This Section highlights the areas where active research is expected to move the science forward within the next 5 years and identifies other aspects that need further attention. The need for continued research and development of metals-specific risk assessment methodology should in no way detract from the expectation of applying sound science to our current way of doing business, as the framework provides substantial guidance on process enhancements that can occur with currently available information.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

2. PROBLEM FORMULATION AND METALS PRINCIPLES

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

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

For metals, the type of assessment (i.e., screening or definitive) and the scale of the assessment (i.e., site specific, regional, or national) will determine how information on metals can be applied in the assessment. Site-specific assessments will involve only a single geographical area of concern and, therefore, can incorporate locally relevant aspects of environmental chemistry, natural background concentrations, and species sensitivies. For regional and national-scale assessments, more general assumptions about the form of the metal in the environment, uptake and bioavailability parameters, and sensitive species or subpopulations are useful, frequently producing results that are conservative in their assumptions in order to be protective of sensitive species or locations. Regardless, the fundamental principles that determine the form of metal in the environment and, consequently, the transport of metals through environmental media to accumulate or cause toxic responses in biota should be considered in all risk assessments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

2.1. PRINCIPLES OF METALS RISK ASSESSMENT

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

Metals Principles

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

2.1.1. Environmental Background Concentrations

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

Background

Background is defined as the amount of metals occurring in soil, water, air, and biota as a result of anthropogenic and natural processes. Anthropogenic contributions are limited to those that are not influenced by current, direct releases (i.e., emissions, discharges, or disposal) from a source or site of concern. This includes metals that may arise from manmade substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that is not specifically related to the release in question (U.S. EPA, 2003e).

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

2.1.2. Essentiality

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

As a practical matter, essentiality sets a lower bound on the range of metal exposures to be considered with respect to the potential for toxic effects. The following discussion highlights the issue of essentiality; further discussion is found in Sections 4.3.2 and 4.5.1. Seven metals are

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

known to be nutritionally essential for humans, and four others have been shown to have possible beneficial effects (Table 2-1); these are reviewed in detail in Goyer et al. (2004). Plants and other animals also depend on certain metals (See Table 4-14), and thus the generalizations about essentiality apply for these organisms as well. The list of metals with no known beneficial human health effects is longer, and some examples are given in Table 2-1.

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

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

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

2.1.3. Environmental Chemistry

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

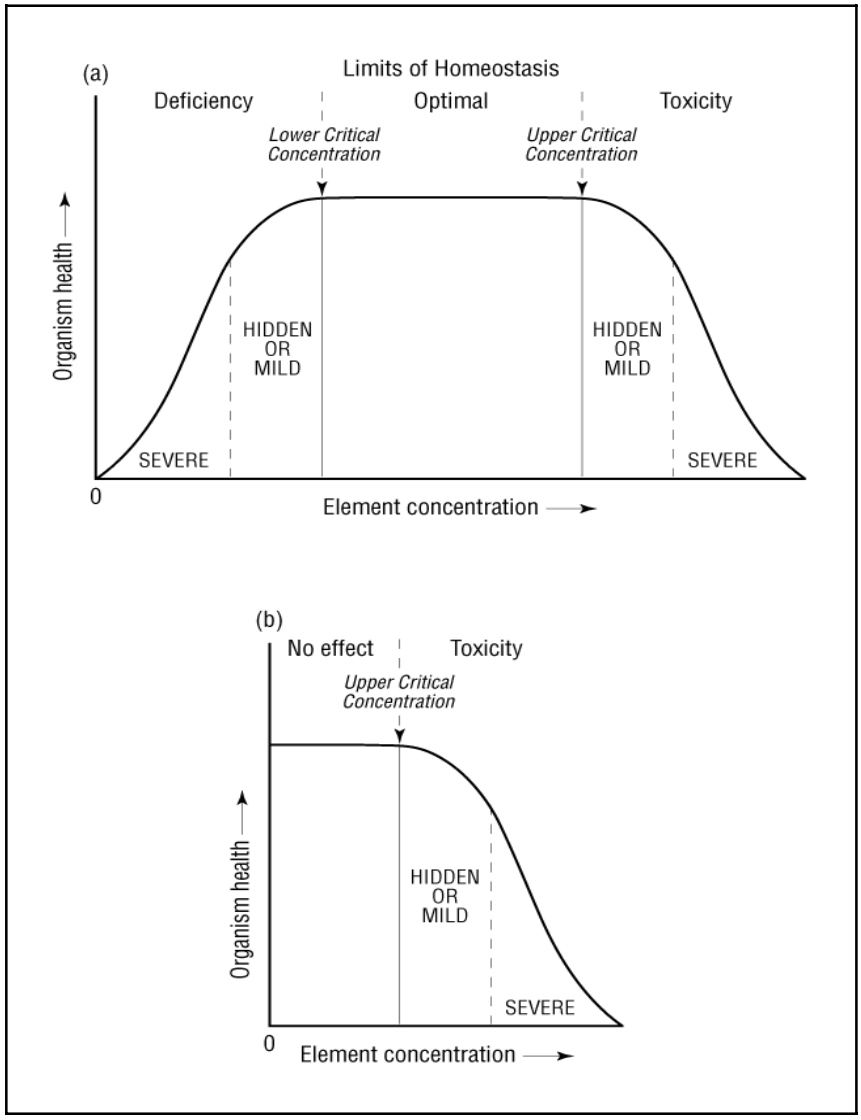

Figure 2-1. Health effect curves for (a) essential elements and (b) nonessential metals.

Source: Fairbrother and Kapustka, 1997.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

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

2.1.4. Bioavailability

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

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

The bioavailability issue paper authors (McGeer et al., 2004) provided EPA with some

Bioavailability, Bioaccessibility, and Bioaccumulation

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

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

Bioaccumulation of metals is the net accumulation of a metal in the tissue of interest or the whole organism that results from exposure from all environmental sources, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a steady-state balance of losses from tissue and the body.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

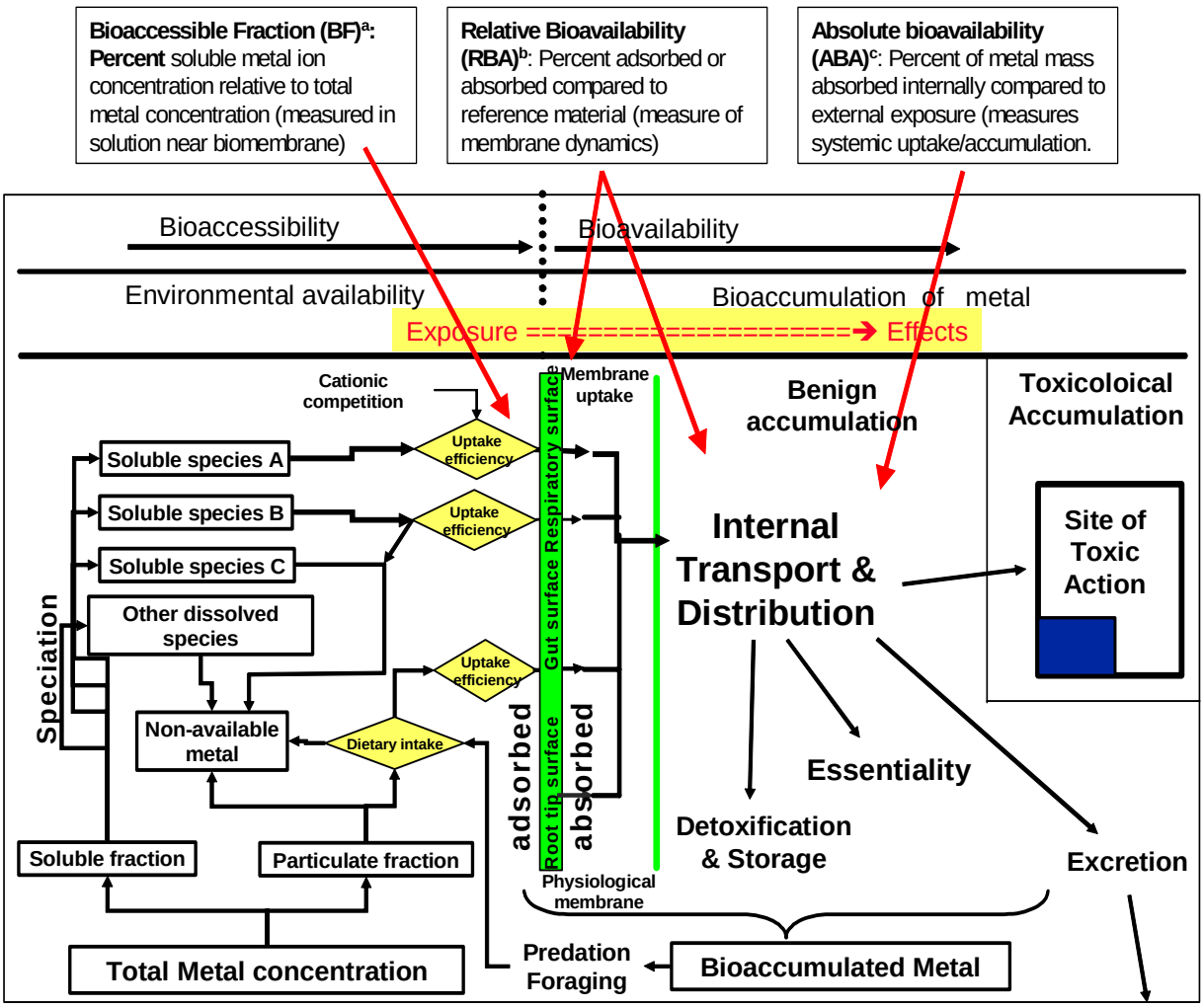

Figure 2-2. Conceptual diagram for evaluating bioavailability processes and bioaccessibility for metals in soil, sediment, or aquatic systems.

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

[b]RBA is most often estimated as the relative absorption factor, compared to a reference metal salt (usually calculated on the basis of dose and often used for human risk, but it can be based on concentrations).

[c]ABA is more difficult to measure and used less in human risk; it is often used in ecological risk when estimating bioaccumulation or trophic transfer.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

2.1.4.1. *Bioaccessibility or Environmental Availability*

The portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (e.g., fate, transport, bioaccumulation) is termed the *environmentally available fraction*. Environmentally available metal is not sequestered in an environmental matrix, and it represents the total pool of metal in a system that is potentially bioavailable to (able to contact or enter into) an organism. The *bioaccessible fraction* of metal is the portion (fraction or percentage) of environmentally available metal (e.g., <250 μm diameter for vertebrates) that actually interacts at the organism's contact surface and is potentially available for absorption or adsorption (if bioactive upon contact) by the organism (see Figure 2-2).

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

2.1.4.2. *Bioavailability*

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

2.1.4.3. *National Research Council Report*

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

2.1.5. Bioaccumulation and Bioconcentration

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

Because plants and animals have evolved in the presence of metals, some of which are required for proper physiological functioning, they have developed a variety of physiological and anatomical means to regulate the amount of metals in their tissues. For some metals, this includes storage in various compartments (e.g., lead in bone or cadmium in kidney). Such bioaccumulation of metals may cause no effects or may eventually result in a toxic response. Should the organism be eaten by another (e.g., an herbivore eating a plant that has stored metal in its foliage or a predator eating a mollusc that has accumulated metal granules), the stored metal may (or may not) result in toxicity to the consumer, depending on the form in which it was stored. Therefore, the mere presence of a metal in an animal or plant cannot always be used to infer toxicity to either the organism itself or to its consumers. If the concentration of metal in an organism is greater than the environmental media (soil, water, or sediment), then the metal is said to *bioconcentrate*. If the organism's metal burden is from *both* environmental media and food intake, then the metal is said to *bioaccumulate*. *Biomagnification* occurs in the food web if each trophic level has a higher amount of metal than the one below it. This occurs readily for

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

persistent organic substances that are highly lipophilic, but generally it is not the case for metals. Organisms at all trophic levels have developed mechanisms to regulate internal metal concentrations and generally exhibit toxic effects and die before tissue levels become very high. Exceptions are organometallic compounds such as methyl mercury or organoselenium and the specialized metal hyperaccumulating plants that use metal storage as a means of detoxifying their environment or discouraging feeding by consumer organisms.

2.1.6. Acclimation, Adaptation, and Tolerance

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

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

Tolerance, Acclimation, and Adaptation

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

2.1.7. Toxicity Testing

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

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

2.1.8. Mixtures

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

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

Metals are normally found in the environment as mixtures with other metals as well as organic compounds. Two key questions should be asked when assessing metals mixtures. First: To what extent does each metal contribute to any observed joint effect? (Recognize that when

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the relative compositions of metals in the mixture change, this change the answer.) Second: Are the effects significantly greater or lesser than the sum of the individual component effects? Some metals can exert a protective or sparing effect when combined with others, thereby mitigating risk (antagonistic) while others can enhance the toxic effect (synergistic). For example, zinc may mitigate mercury toxicity, and copper may have a protective effect against cadmium poisoning, while copper deficiency can enhance the effects of lead.

2.2. METALS CONCEPTUAL MODEL

The relationships between the sources, exposure, and effects of metals to human and ecological receptors are complex and specific to the site, environmental condition, and receptor organism. Because metals are naturally occurring substances, transition functions between environmental loadings, media concentrations, exposed receptors, and the final organismal or ecosystem responses are affected by natural processes to a much greater extent than occurs with xenobiotic organic contaminants. These transition functions should be specifically identified in the conceptual model for all metals assessments.

A conceptual model depicted in Figure 2-3 shows the interrelationship between the metals or metal compounds of interest and the assessment process. It is a representation of the actual and potential, direct and indirect relationships between stressors in the environment and exposed humans (or particular subpopulations) or ecological entities. The model depicts possible pathways from sources of metals to receptors and includes environmental or biological processes that may influence the predominant route of exposure or the physical/chemical properties of the metal compounds.

The goals and scope of an assessment, in addition to the availability of data, methods, and resources, are among the most important factors that determine the extent to which key metal principles should be incorporated into an assessment. Generally, assessment endpoints are selected during the problem formulation phase of all risk assessments based on their relevance to management goals, societal values and laws, known adverse effects of metals, and endpoints of importance to stakeholders. Risk assessors will incorporate metal principles to a lesser extent in screening level assessments than in definitive risk assessments. Site-specific assessments can account for more metal-specific processes (particularly, environmental chemistry) than can national-level assessments that require generalization across multiple ecoregions. Therefore, it is recommended that, when appropriate, regional- or national-level risk assessments be subdivided into metal-related ecoregions, known as “metalloregions” (McLaughlin and Smolders, 2001), such that protection levels, mitigation goals, and ranking results will be appropriate for the suite

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of species naturally present within each type of controlling environment. This is directly analogous to the use of ecoregions when establishing water quality criteria (Griffith et al., 1999). The problem formulation phase of the assessment should clearly identify whether a regional approach is being used and, if so, how the metalloregions are defined in terms of species composition and environmental controlling factors.

This concept of regional-based ecological assessments is significantly less important in human health assessments. In these assessments, the environmental controlling factors (pH, water hardness, etc.) may be important determinants in exposure calculations for dietary or drinking water exposures. However, humans have not adapted to particular areas of metal enrichment or impoverishment but, rather, choose to live in all environments. Therefore, the differences in human sensitivity that should be considered are not geospatially correlated. Rather, consideration should be given to the identification of potentially sensitive subpopulations, such as the very young or the elderly, those with genetic predispositions to metal sensitivity (e.g., Wilson's disease), or other similar groups (see Section 4.3, Human Health Effects). Again, the problem formulation phase should clearly state whether the risk results will be applied on a population-wide basis, such that protection is afforded to the most sensitive individuals, or whether these groups are given additional scrutiny and separate risk analyses, such that results will be applicable only to the general population.

Areas in the conceptual model that stand out as metal-specific issues are identified in Figure 2-3 as the transitions between environmental loadings, media concentrations, exposure receptors, and the final organismal or ecosystem risk. Because metals are naturally occurring substances with which organisms have evolved, it is particularly important to incorporate into the risk assessment the natural processes that affect metal mobility, speciation, sequestration, and toxicity. These may differ in details or approach, depending on the environment of concern (water, land, air), the final receptor organisms (humans, animals, plants), and whether the management goal is health of individuals or maintenance of populations and communities of organisms. However, the same basic concepts always arise, regardless of the assessment context.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

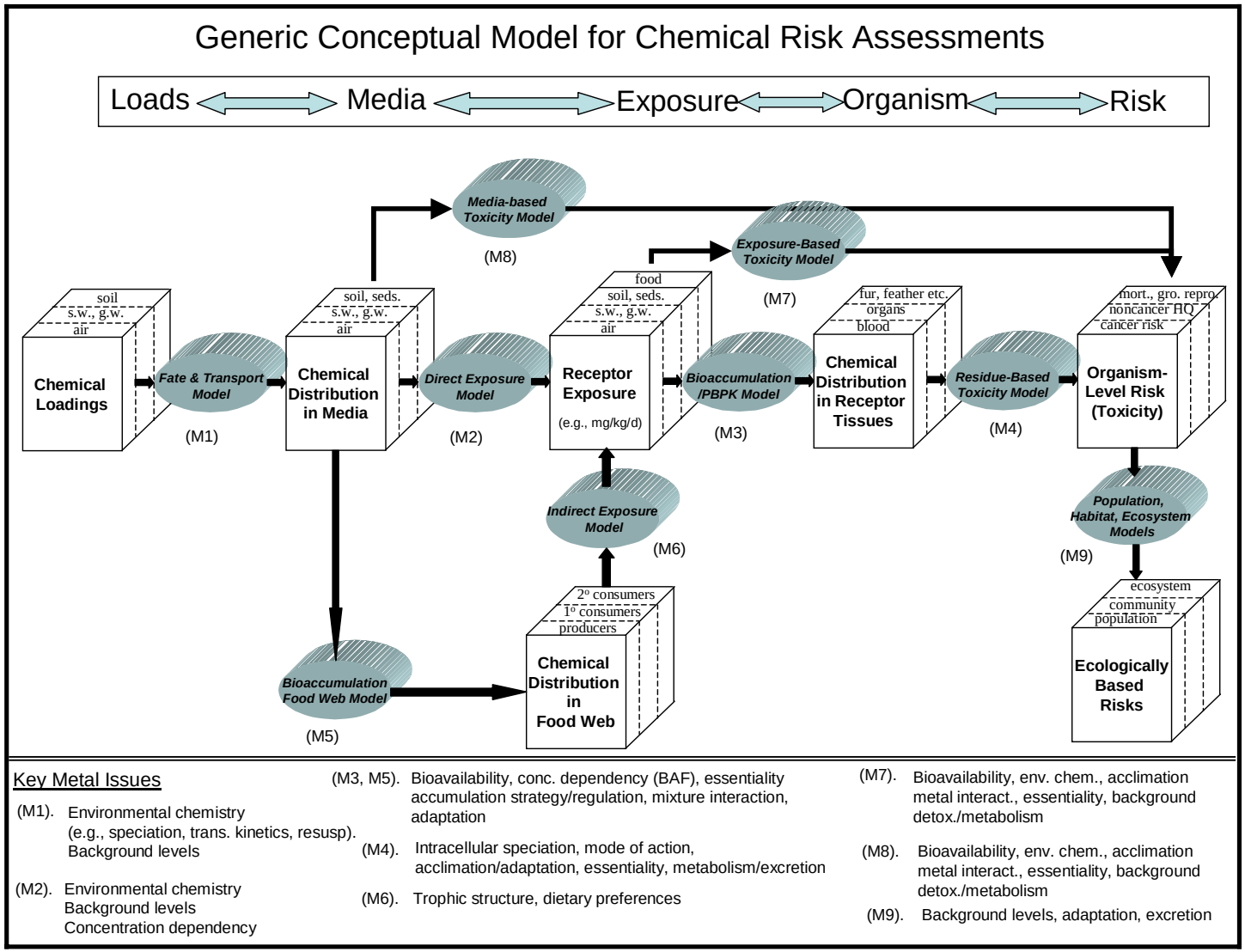

Figure 2-3. Generic conceptual model for metals risk assessment.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

- **Environmental chemistry (M1).** The partitioning of the metals or metal compounds of concern into the various environmental media from the loading source is dependent on the physical properties of the initial form of the material and the particular chemistry of the receiving environment. Models are useful to estimate speciation, transition kinetics, and potential resuspension of the material within the context of natural background levels of the metal and other inorganic substances. These can be very detailed for site-specific assessments, or they can provide a potential range of processes that might occur over large regional scales for assessments of a more generic nature (e.g., criteria development or ranking schemes). The degree of influence of various environmental attributes on the final distribution of the metals of concern into the various media also can be identified through the application of appropriate models.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- **Residue-based toxicity models (M4).** If risk to the organism(s) of concern is to be based on an estimate of internal dose, then information about the relationship of whole-body (or target organ) residue levels to toxic responses should be understood, either from empirical data or PBTK/toxicodynamic models. Because of the processes discussed in the previous paragraph, this can be particularly challenging for metals. Metal speciation in the exposure matrix can significantly influence this relationship because uptake and organ distribution kinetics are likely to differ.

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

- **Indirect exposure model (M6).** The exposure of an organism of concern is dependent on its location within the trophic structure of the community and its dietary preferences. Although this node of the conceptual model differs very little from risk assessment approaches for organic substances, some metal-specific generalities about the relative importance of exposure pathways can be applied to focus (and simplify) the process.

- **Exposure-based toxicity model (M7).** Calculation of appropriate external dose (oral intake, gill binding, etc.) for comparison with toxicity thresholds depends on information about relative bioavailability (RBA), speciation of the metal or metal salt, dietary preferences and rates, natural background concentrations, essentiality, and metal interactions. Toxicity threshold considerations should be based on comparable information, such as appropriate metal species in exposure media, similarly acclimated or adapted organisms, similar exposure routes, and appropriate combinations of essential metals.

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

- **Population, habitat, ecosystem models (M9).** Ecological risk assessments often ask questions related to population growth, habitat change, or ecosystem functions in addition to questions related to risks to individual organisms. Most of the models and approaches are similar for both metal and organic substances. However, metals and

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

other inorganic substances are among the fundamental determinants and delimiters of ecoregions (in conjunction with climate, elevation, and day length associated with latitude). Therefore, a knowledge of natural background and adaptation of organisms to differing metal levels is essential in developing appropriate risk factors for naturally occurring species.

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

2.3. NEXT STEPS

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3. METALS RISK ASSESSMENT RECOMMENDATIONS

The metals risk assessment recommendations are a formulation of the primary concepts and factors that should be considered when conducting assessments of the ecological or human health risks associated with metals exposures. The fundamental metals principles, outlined in Section 2.1, that should be considered throughout metals risk assessment are integrated into these recommendations as appropriate. The recommendations are not intended to provide a prescriptive step-by-step guide on conducting metals risk assessment. Rather, they are intended to promote the consistent application of the various tools and methods currently available to risk assessors so that assessments take into consideration the unique properties of metals. Moreover, these recommendations are presented with the intent that they be used in parallel with currently available Agency guidance for human health and ecological risk assessment.

Section 4 provides the risk assessor with an expanded discussion of the underlying issues and methods that form the basis for the recommendations in Section 3. In addition, the metals recommendations rely on the final metals issue papers, which have been developed by scientists commissioned under contract by EPA to identify current information, tools, and methods in metals science. The final metals issue papers are available on the EPA Web site at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119. Section 5 reviews research needs based on the limitations in the currently available tools and methods; it also reviews gaps in our understanding of metals behavior and effects on humans and the environment.

3.1. HUMAN HEALTH RISK ASSESSMENT RECOMMENDATIONS

Assessing the risks of metals to human health is similar to conducting assessments of organic substances. However, risk assessors should pay particular attention to the metal-specific principles discussed in Section 2. These include the influence of environmental chemistry on speciation, bioavailability, natural and ambient background levels of metals in the environment, and the ubiquitous presence of metal mixtures. Additionally, certain properties associated with toxicokinetics and toxicodynamics, carcinogenesis and non-cancer, and the sensitivity of particular subgroups, are unique to metals and should be incorporated into the risk assessment process. Data from standard toxicity tests should be interpreted appropriately in light of these metal-specific attributes. Tools are available for addressing most of these metal-specific attributes to one degree or another during a human health risk assessment.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3.1.1. Fate and Transport

Transport or movement of metals through the physical environment (soil and sediment, surface and ground water, and air) is a function of the source characteristics (e.g., discharge point), the nature of the metal species or compound (e.g., chemically reactive or recalcitrant; dissolved, complexed, or solid/precipitate), and the physical/chemical characteristics of the receiving environment. Generally, the fate and transport of metals are not greatly affected by macrobiota (e.g., via tracking), but the influence of local microbial processes can be significant (including mobilization in the root zone, and methylation) (see Section 4.1.9) Therefore, such analyses are equally relevant to human health and ecological risk assessments. Consequently, recommendations pertaining to the fate and transport of metals are provided in Section 3.2. for the aquatic environment (e.g., water, sediment, associated biota), and in Section 3.3. for the terrestrial environment (e.g., air, soil, associated biota).

3.1.2. Exposure Assessment

Assessing human exposures involves evaluating how people can be exposed to metals and in what amounts. Specific steps include (1) identifying the forms (speciation) and concentrations of metals in the media to which people are exposed (e.g., soil, water, air, or biota, accounting for setting-specific biogeochemical conditions); (2) describing how people contact these media, by what specific routes they are exposed (e.g., incidental ingestion or inhalation); (3) determining the appropriate exposure metric (e.g., oral intake, air concentration, or blood concentration), and quantifying that metric (e.g., estimating the amount ingested, or determining the blood concentration); and (4) characterizing the uncertainty and natural variability associated with these estimates, where possible.

3.1.2.1. *Background*

Metals, being part of the periodic table of the elements, constitute a portion of the natural background to which all humans are exposed. Metals are an important constituent of the diet and the Earth's crust. For example, 95% of the general population's exposure to copper is through the diet, and concentrations of natural levels of organic arsenicals in seafood can be sufficiently high to cause the urinary arsenic concentration to resemble that of an occupational exposure. Risk assessments addressing anthropogenically introduced metals should separate such introductions from natural levels, or levels associated with other contributions beyond the scope of the assessment, and account for the possibility of cumulative exposure. The former is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

critical for informing risk management decisions. The latter, considering cumulative exposures, is technically challenging because of potential differences between the bioavailability of naturally occurring metals and anthropogenically introduced metals. In addition to the human health-specific recommendations that follow, risk assessors are encouraged also to refer to the background discussion in the terrestrial risk assessment recommendations (Section 3.3) as it is applicable to human exposures.

Recommendations:

- Consideration of background exposures is important in risk assessments and may have a variety of aspects. For example, when considering soil ingestion pathways, if feasible, it is important to account for the potential differences in the bioavailability of naturally occurring metals and metals more recently introduced via anthropogenic activities. See section 4.5.4 for further discussion.

- If blood, urine, or other tissues are being used to assess exposure to a metal from a particular source (e.g., arsenic in drinking water), consideration of other contributing exposures is important.

3.1.2.2. *Air Pathway and Inhalation Exposure*

For most metals, inhalation exposure is to metals associated with particles. For particle size exposures, the size of the particles is an important factor in potential for respirability, subsequent dosimetry and health risk. The particle size of interest for inhalation exposure is generally those particles less than or equal to 10 microns in diameter (PM_{10}); larger particles do not penetrate far into the respiratory tract and can be cleared to the ingestion route. Additionally, toxicity of a metal can vary depending on its valence state or with the compound. In developing inhalation exposure estimates, attention should be given to the form of metal as compared to the form used in the dose-response assessment (e.g., RfC, IUR). Measuring or estimating the total amount of a metal without regard to speciation may introduce uncertainties into inhalation exposure and risk. See Section 4.2.2.2 for further discussion.

Recommendations:

- For inhalation assessments for metals that rely on monitoring data (e.g., using area or personal samples), consideration of particle size is important, and the primary focus generally should be on metals associated with particles that are less than or equal to 10 microns in diameter (PM_{10}).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- As feasible, inhalation exposure estimates should be specific to the metal speciation in order that there can be pertinent correspondence with the form of the metal used for the dose-response assessment (e.g., in deriving the RfC or IUR estimate).

3.1.2.3. *Soil, Dust, and Dietary Exposure Pathway*

Humans can be exposed to metals in soil and dust primarily via incidental ingestion, or via inhalation. Diet plays a dominant role in common human exposures to metals (via plant and animal uptake and food chain transfer). The dermal pathway is not considered a major pathway for metal intake because the relatively low lipid solubility of most metals limits absorption through the skin. However, some metals may produce skin toxicity (e.g., allergic contact dermatitis), which would require consideration of dermal exposure. See Section 4.2.2.3 for further discussion.

Recommendations:

- Owing to relatively low lipid solubility of most metals, dermal absorption from soil and dust is generally low and could be ignored in most metal assessments.

- Depending on the exposure situation, portal of entry dermal sensitization can be an issue. The assessor should consider dermatitis at least in a qualitative sense as a health endpoint of concern, particularly for nickel, chromium and arsenic.

- Exposure from incidental soil or dust ingestion should be adjusted for bioavailability before adding to intake from oral exposure pathways (U.S. EPA, 2004a). See Section 4.2.4 for further discussion.

- Concentrations of metal in food (i.e., dietary intake) should be adjusted to account for relative bioavailability differences; a default value of 100% can be used for metals that are biologically incorporated in food. For diets that contain metals deposited onto food (e.g., dust or other particles), bioavailability should be assumed to be the same as metals in soil. See Section 4.2.4 for further discussion.

3.1.2.4. *Water Pathway and Oral Exposure*

Humans consume water specifically treated for human consumption (i.e., drinking water); thus, the exposure context of metals in human drinking water will be very different from that of exposures to ambient water. Inorganic forms of metals in drinking water will consist of the more bioavailable, water-soluble species.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Estimation of intake of metals in drinking water requires information about concentrations of metals in the finished water and the amount of water consumed. Metal concentrations in drinking waters are measured at the distribution point for municipal water delivery systems. The contribution of metals from pipes (either from the distribution system to the home or within the home) is rarely assessed. Water delivered from private wells or ambient surface waters may contain higher levels of organic carbon or other ligands to which metals can bind, thereby requiring an adjustment to account for differential bioavailability of the dissolved metals. These factors can be incorporated into site-specific assessments, but local data will need to be collected on a case-by-case basis. See Section 4.2.2.5 for further discussion.

Recommendations:

- Regional differences in bioavailability of metals due to variation in water characteristics (e.g., hardness), the contribution of household distribution systems to total metal load at the tap, and lack of information from households on private wells should be included as uncertainties in national-level risk assessments.

- It is recommended that site-specific assessments use measured metal concentrations at the tap.

- Although people can be exposed to metals dissolved in ambient surface water during swimming, other recreational activities, or various occupational activities, dermal absorption can be considered a negligible exposure pathway.

3.1.2.5. *Integrated Exposure Approaches*

The many pathways that might be associated with metals exposure represent an important consideration for the risk assessor. For lead, EPA has developed the Integrated Exposure Uptake Biokinetic (IEUBK) model to address these pathways. The model simulates the transfer of lead into the blood, with consideration of absorption and elimination as a result of inhalation and oral exposures. Similar models for other metals have not yet been developed. While similar models for other metals have not yet been developed, there are a variety of exposure models that could potentially be applied in metals risk assessment (e.g., SHEDS, DEPM, TRIM, RESHRAD). These models, and their applications and limitations, are discussed in Section 4.2.4.1.

Recommendation:

- The IEUBK model for lead in children is recommended for use in all site-specific assessments. It is available on line at

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

http://www.epa.gov/superfund/programs/lead/ ieubk.htm. The IEUBK model may be used to account for lead accumulation resulting from differential rates of uptake and elimination. This model is not applicable to other metals.

3.1.2.6. *Bioavailability*

Bioavailability of metals is an important consideration in human health assessments, particularly when assessing risk of metals in soil. Metals may form organic complexes in water, bind to soil substrates or be incorporated into soil matrices, or form complexes with food materials, and the bioavailability of the metal in the study on which the dose-response assessment is based (e.g., animal feed, water, or corn oil) may differ from that of the metal in the matrix being assessed (e.g., soil). Different approaches have been used to address bioavailability, depending on the data available. These approaches have been advanced particularly with regard to soil ingestion. EPA's OSWER has developed a relative bioavailability approach to adjust the RfD. Further discussions on bioavailability issues are presented in Sections 2 and 4.2.4.2., and in McGeer et al. (2004), NRC (2002), and U.S. EPA (2004).

Recommendations:

- To address relative bioavailability, the preferred approach is to use information directly relevant to the conditions being assessed, e.g., data from animal toxicology studies that use the metal form encountered in that environment.

- Where this information is not available (e.g., in screening-level assessments), the recommended approach is to assume that the bioavailability of the metal in the medium being assessed is the same as that of the metal in the study on which the dose-response (e.g., RfD, RfC, or cancer slope factor) was based.

- For higher level, definitive risk assessments, a medium-specific default absorption factor for the metal may need to be used, and in such cases the factor should be as representative as possible of the conditions being assessed.

- For lead, the juvenile swine model presently is the preferred animal model to use for development of relative bioavailability factors (U.S. EPA, 2004a).

- When validated, in vitro methods for determining lead relative bioavailability in soils may be used in place of animal studies (U.S. EPA, 2004a).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3.1.3. Effects Analysis

3.1.3.1. *Physiologically Based Pharmacokinetic (PBPK) and Physiologically Based Pharmacodynamic (PBPD) Modeling*

Combined use of PBPK and PBPD models provides understanding of the complex relationships between exposure and target organ effects. These models are valuable risk assessment tools for purposes of interspecies, high dose/low dose, rout to route, and exposure scenario extrapolation. PBPK models that include a fetal compartment are particularly valuable for human health risk assessment of metals, as transplacental exposures cannot be directly measured from environmental measurements. An additional specific recommendation regarding the IEUBK model is provided in Section 3.1.2.5.

Recommendations:

- When using PBPK models or other dosimetric adjustments, absorption/distribution and kinetic factors should be considered explicitly. The models require special considerations for cellular uptake, interaction with nutritionally essential and nonessential metals, protein-binding behavior and function, incorporation into bone, metabolism, and excretion (see Table 4-11 in Section 4.2.6).

- Application of a PBPK model to risk assessment should satisfy the following key criteria: (1) identifying toxic or active form(s) of the metal, (2) selecting the appropriate dose metric, and (3) identifying the appropriate target organ or cells on the basis of the health effect of greatest concern.

- These available models for lead (see section 4.2.6.1) can be used to estimate fetal exposure but are limited in that they rely on assumptions of a steady state between maternal and fetal blood lead concentrations, which is violated if the mother is no longer exposed to lead during pregnancy. This assumption should be stated in the risk characterization.

- Similar models for other metals are not available at this time, so transplacental transfer cannot be estimated for other metals.

3.1.3.2. *Essentiality*

Some trace elements, such as cobalt, copper, iron, and zinc (Table 4-12 in Section 4.3.2), are necessary for biological functions and the normal development of humans, other animals, and plants. These metals are required for organism health at one range of concentrations and can be toxic at higher quantities. For essential elements that exhibit biphasic dose-response curves,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

adverse effects resulting from deficiency should be considered as well as those that result from excessive exposure.

Recommendations:

- In setting reference values (Reference Concentrations [RfCs]/RfDs) the Recommended Daily Allowance (RDA) should be taken into consideration.

3.1.3.3. *Toxicity Testing*

At least five transition metals or metalloids—arsenic (through drinking water exposure), cadmium, chromium VI, beryllium, and nickel (from pulmonary or, in some cases, dermal exposures) — are accepted as human carcinogens in one form or another or in particular routes of exposure (NTP, 2002). Inorganic lead compounds are considered probable human carcinogens by EPA's IRIS program, and IARC has concluded there is limited evidence of carcinogenicity to humans. Target organ sites for metals as carcinogens are summarized by Waalkes (1995). Many noncarcinogenic effects can also be caused by exposures to metals. See Section 4.3.5 for further discussion.

Recommendations:

- It is recommended that metals risk assessments follow the same approach for carcinogenicity assessment as used for all other substances (U.S. EPA, 2003b), with modifications as indicated by unique metal-specific data or methodology that may exist.

- In parallel, the same general approach applied to assess non-cancer endpoints for other chemicals should also be followed for metals, except where modifications are warranted.

For example, an extensive model has been developed to evaluate lead, but a completely parallel model does not exist for assessing a wide range of other metals and other chemicals. For arsenic, unlike many other chemicals, the standard toxicity test data for rodents are not the primary basis for assessing human toxicity.

3.1.3.4. *Metals Mixtures*

Metals are normally found in the environment as mixtures, and risks may be mitigated or enhanced by any associated interactions. There are generally three classes of interactions between metals: (1) between nutritionally essential metals; (2) between non-essential metals;

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

and (3) between essential and non-essential metals. Additionally, the relative dose and mixture composition, as well as mode of action of each metal in the mixture, is especially important in determining overall health consequences. One form of interaction, termed "molecular" or "ionic" mimicry, is an important consideration in evaluating the health effects of metals. Selenium, for example, may play a protective role with regard to ingested arsenic. See Section 4.3.6 for further discussion.

Recommendations:

- For metal mixtures, as for other mixtures, the assessor is referred to EPA's guidelines and supplemental guidance for the assessment of mixtures (US EPA, 1986a; US EPA, 2000b).

- Unless other information is available, the default approach is to assume dose additivity for individual metals that produce the same effects by similar mode of action.

- In the case of metals with known differences in critical effects, separate effect assessments are encouraged for each metal. Interactive effects (e.g., synergism, antagonism) should be included if information as available or acknowledged as a source of uncertainty.

- While additional research is needed to explore the issues of metal mimicry and its effect on assessment, site assessments should consider the available information on metal mimicry related to the metal(s) of interest, including that referenced in this framework.

3.1.3.5. *Sensitive Subpopulations and Life Stages*

Metals have a relatively robust literature on susceptible populations. For example, the efficiency of intestinal uptake of zinc declines in the elderly, absorption of cadmium may be greater in premenopausal women with depleted iron stores, and various genetic polymorphisms have been associated with the effects of metals, including copper, iron, lead, and nickel. See Section 4.3.7 for further discussion.

Recommendations:

- For metals, as with other agents, Agency risk assessments should consider subpopulations with differing sensitivities that may arise as a result of differential exposure or susceptibility.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3.2. METALS RISK ASSESSMENT RECOMMENDATIONS FOR AQUATIC ENVIRONMENTS

This section presents recommendations for assessing exposure and effects of metals in aquatic systems. Many of the suggested methods for fate and transport apply to human as well as ecological risk assessments. Recommendations given are specific to aquatic biota residing in the water column and sediments, unless otherwise noted. Particular methods and models described in the recommendations are discussed in more detail in Section 4.4, the metal issue papers, and referenced citations.

3.2.1. Fate and Transport

Approaches for evaluating the fate and transport of metals in aquatic environments include measurements and models. Selection of methods will depend on the nature and scale of the problem. For example, for applications where metals have already been released to the environment (e.g., at a hazardous waste site), measurements of the distribution of the metals among environmental compartments is often an important starting point for the assessment. For applications where decisions need to be made on wasteload allocations, such as for determination of Total Maximum Daily Loads (TMDLs), models play a central role; these are typically supported by measurements. For national assessments, generic models that capture a range of conditions may be most appropriate. A suite of measurement and modeling tools exists. Selection of the most appropriate combinations should be commensurate with the problem at hand. In many cases, relatively simple approaches will suffice, and in others more sophisticated methods are warranted. A complicated model is not necessarily a "better" model to use than a simple one; the appropriateness for use of a specific model needs to be decided on a case-by-case basis.

Measurement programs that support evaluations of fate and transport are addressed in other Agency guidance and are not addressed here; however, these should be considered an appropriate part of assessments. Measurement approaches for evaluating the bioavailability of metals are discussed later in this subsection. Recommendations related to the use of fate and transport models for the assessment of metals in aquatic environments are provided below.

An important parameter in modeling the transport and fate of metals in aquatic systems is the partition coefficient. The partition coefficient sets the distribution of the metal between the dissolved and sorbed phases; this, in turn, has important implications to the magnitude of particulate and diffusive transfers between the water column and sediment, and in assessing

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

metal bioavailability. However, assuming equilibrium conditions is a potential oversimplification in some situations (e.g., in the vicinity of a point source discharge to a receiving water or during a pulse exposure), and this could be a significant source of uncertainty in the exposure assessment. See Section 4.4.1 for further discussion.

Recommendations:

- The reviews by U.S. EPA (1997) and Paquin et al. (2003), 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. These reviews also include descriptions of example applications of many of the models that are discussed. These reviews and Section 4.2.2.1 provide a good starting point for selecting among available models.

- Relatively simple steady-state and analytical solution models may be appropriate for use in the screening level. Use of conservative assumptions at this level of analysis may provide insight about whether or not it will be necessary to complete a more detailed, definitive risk assessment.

- Relatively complex and sophisticated time-variable models are appropriate for use in higher level, definitive assessments. These models, in particular, should always be used by an analyst who is experienced in the use of models and familiar with the structure of the model being employed. Predictions of fate and transport of metals in aquatic systems may be accomplished by using integrated models that include hydrodynamic, sediment transport, and chemical transport algorithms, or by using stand-alone hydrodynamic and/or sediment transport models that should then interface with a chemical fate model. 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 intervention by the analyst. This is in contrast to use of the stand-alone models, where the output of one model needs to be formatted in such a way that it is amenable to use by the subsequent models that are to be applied. An advantage of the latter approach is that it can in some instances reduce the need to rely on lengthy model run times.

- Most of the available transport models do not currently include chemical speciation subroutines. In such cases, chemical equilibrium models such as MINTEQ serve as useful alternatives for characterizing the forms of the metal that are present.

- Water quality analyses often require probabilistic results, as the Water Quality Criteria (WQC) specify not-to-exceed concentrations for a once-in-3-year return period. Steady-state models are not directly amenable to evaluation of a return period for WQC exceedences. When using these models, a Monte Carlo analysis can be conducted to generate a large number of model inputs and subsequent solutions,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

which can then be analyzed statistically to characterize the probability of an exceedence of the effect level of interest. Time-variable models that generate long-term time series results (e.g., 20 years) can also be statistically analyzed to evaluate the frequency of exceedences.

- The risk assessor should consider the potential for situations where nonequilibrium conditions exist, as this may have important implications to the partitioning of a metal between dissolved and particulate phases and to the characterization of metal speciation and bioavailability that is provided by a chemical equilibrium model (see Section 4.1.4).

- An important parameter in modeling the transport and fate of metals in aquatic systems is the partition coefficient. The partition coefficient sets the distribution of the metal between the dissolved and sorbed phases; this, in turn, has important implications to the magnitude of particulate and diffusive transfers between the water column and sediment, and in assessing metal bioavailability. However, assuming equilibrium conditions is a potential oversimplification in some situations (e.g., in the vicinity of a point source discharge to a receiving water or during a pulse exposure), and this could be a source of uncertainty in the exposure assessment. See Section 4.1.4 for further discussion.

- Special care should be taken when modeling metals (e.g., chromium) and metalloids (e.g., mercury and arsenic) that can readily change oxidation state or undergo transformation. Such changes affect physical and biological properties. Although many of the same transport models can be used, input parameters will require modification.

3.2.2. Water Column Exposure, Bioavailability, and Effects

Potential exposure routes for aquatic species include inhalation/respiration, dermal absorption, and dietary (from either food or incidental sediment ingestion). However, owing to the diversity of aquatic organisms, the extent to which a metal is taken up by any one of these exposure routes is difficult to define for all relevant routes. With those limitations in mind, most of the focus on exposure and effects has been on the binding of metals to the gill surface for short-duration exposures and the resultant toxicity.

Approaches for evaluating exposure and effects include measurements and chemistry-based exposure models. Laboratory and in situ toxicity tests and field assessments of biota have all been used to evaluate metals. These will continue to have an important place in developing chemical-based methods and in assessing conditions at particular water bodies. These approaches have been described in other Agency guidance and are not repeated here.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Accounting for bioavailability should be an essential part of metal assessments; however, a host of factors can influence the amount of metal that interacts and is taken up across biological surfaces, and water quality can have a dramatic influence on toxicity. Depending on the level of assessment, different methods and approaches can be used to incorporate bioavailability.

Ambient Water Quality Criteria (AWQC) are developed to support the Clean Water Act, and since the 1980s aquatic life criteria for several cationic metals have been expressed as a function of water hardness to address the relationship of certain cations on toxicity. However, water hardness adjustments do not account for other important ions and ligands that can alter metals bioavailability and toxicity. The Water Effect Ratio (WER) was developed in the 1990s to address this issue directly. This is an empirical approach to make site-specific bioavailability adjustments to criteria (U.S. EPA, 1994). This approach relies on comparing toxicity measurements made in site water 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.

Recent developments in understanding the physiology and toxicology of metals have enabled further advances in incorporating bioavailability into assessments. Different forms of the dissolved metal have differing bioavailabilities; free metal ions generally are the most bioreactive, and complex forms generally are much less so. The relationship between speciation and bioavailability has been developed as the Free Ion Activity Model (FIAM) (Campbell, 1995), and geochemical modeling software such as CHESS, MINEQL, WHAM, and MINTEQ are powerful tools in understanding speciation. The development of speciation profiles for a dissolved metal concentration via modeling and/or direct measurement will help to provide information at a particular site of interest and can be used on a comparative basis between sites to reduce the variability associated with different exposure conditions.

Although the link between bioavailability of metals and factors influencing speciation (such as pH, temperature, and organic and inorganic anionic complexation) are of prime importance, other abiotic factors, particularly cations, influence metal bioaccumulation and toxicity. Dissolved cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+} can competitively inhibit metal uptake and the recent development of integrated toxicity prediction models. Biotic Ligand Models (BLMs) have successfully combined abiotic speciation, cationic competition, and bioaccumulation at the presumed site of toxic action (as reviewed by Paquin et al., 2002).

Applicability of the BLM is being extended to chronic toxicity through, for example, the use of the Ion Balance Model (IBM) of Paquin et al. (2002a, b, c). Although the approach,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

which was initially applied to silver, may ultimately provide a way to predict effects due to metals over varying exposure durations, further development and testing are required.

Overall, the BLM approach has wide application in terms of understanding bioavailability in relationship to toxicity because it incorporates speciation in the exposure medium, bioaccumulation, and toxic impacts in a robust approach that has been possible to apply in a variety of contexts to account for differences in bioavailability. For example, the BLM has recently been incorporated as part of the revision of the WQC for copper, it has been used in the context of risk assessment, and it is being applied as an alternative to the application of WER approaches for setting site-specific discharge and cleanup objectives. When considering the application of this approach, as with all models, care should be taken to understand and explicitly account for the assumptions and potential sources of uncertainty. It should be recognized that the BLMs are being developed only for a subset of metals (e.g., copper, nickel, cadmium, silver, lead, and zinc) and are based on experimental data from a limited number of test species. Additionally, most BLMs predict acute toxicity, although a few are being developed that predict chronic toxicity (e.g., the IBM). Considerable research efforts are ongoing, and it is likely that our understanding of metal bioavailability and the method for integrating this knowledge into prediction models will improve quickly in the coming years. See Section 4.5.7 for further discussion.

Recommendations:

- Methodologies for evaluating the bioavailability and toxicity of metals in water include hardness adjustments, site-specific WERs, and use of the FIAM and BLM. Selection of an appropriate approach will depend on the metal of interest and the availability of data. The FIAM and BLM have been shown to offer dramatic improvements over traditional approaches, and these models are preferred for metals for which adequate supporting data have been developed.

- Hardness should be used as a normalizing function for metal toxicity only when information on speciation is lacking.

- The BLM offers a mechanistic approach for relating the bioavailability of metals to toxicity. It can be used to develop or revise water quality criteria (e.g., as in the case of copper), in risk assessments, and as an alternative to the WER approaches for setting site-specific discharge objectives.

- Quantitative Ion Character Activity Relationships (QICARs) are available for select species and may be used to extrapolate availability and/or toxicity for a metal for

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

which data are limited. However, the QICAR approach may require validation prior to each application.

3.2.3. Background

Background concentrations of metals may contribute to and exacerbate toxicological effects and accumulations of metal from various exposure sources or, conversely, it may result in adaptation of organisms to higher metal concentrations and result in increased tolerance to exposure. Thus, consideration of background metal concentration is an important part of risk assessment.

Concentrations of metals in waters of the U.S. vary tremendously. Thus, use of a single number to represent all areas within the U.S. is discouraged. See Sections 4.5.4.1 and 4.5.4.2 for further discussion.

Regarding the discussion on the 'added risk approach", this approach has been used in Europe, but has recently been reported to be unreliable by the European Commission Health and Consumer Protection Directorate General, Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE) (equivalent to EPA SAB) (EC Health and Consumer Protection/CSTEE, 2004). They report: "The CSTEE is of the opinion that current knowledge on the geographic distribution of metal background concentration in aquatic systems is insufficient to correctly implement the added risk approach… and,.. not accounting for bioavailability in both the MPA (maximum permissible addition, i.e., water quality criteria as an amount added to background) and Cb fraction (background fraction) results in the incorrect assessment of the risks of metals and thus prevents the establishment of science-based EQS (environmental quality standard). The CSTEE suggests that an accurate assessment of the risks (or EQS) posed by metals should be done by establishing - on a site-specific-, watershed/basin- or regional basis - both the bioavailable total fraction in the environmental compartment/medium ($Ec_{bioavailable}$ - background) and the bioavailable total no effect concentrations ($PNEC_{bioavailable}$)."

Recommendations:

- While work is underway to define average (and ranges) of background concentrations for ecoregions, the recommended default is to use state averages where possible and to always define the range that might be encountered within the spatial scale being considered. See section 4.5.4.1 for further discussion.

- For site specific assessments, a physical and/or temporal boundary needs to be defined then background should be described, estimated, or measured. (See section 4.5.4.1 for more information.)

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Although consensus on a methodology has not been reached at this point, it is recognized that the bioavailability of the background , as well as the anthropogenic contribution, should be assessed in terms of both exposure and impact.

3.2.4. Bioaccumulation

Characterization of metal bioaccumulation is an important component of many Agency assessments that range in complexity (i.e., from screening-level to definitive assessments) and overall scope (i.e., from to site-specific assessments to national ranking and characterization). Assessments may consider bioaccumulation either in terms of the potential for the metal to directly affect the organism and/or as the basis for estimating exposure to consumers via a trophic pathway. Understanding this component is relevant for ecological risk assessments, and also for human health assessments when the food chain pathway is involved.

The prevalence and importance of bioaccumulation in Agency assessments has brought increasing attention on the scientific validity and uncertainty of the methods used to characterize and quantify metal bioaccumulation. To reduce uncertainty in metals assessments, robust connections should be established 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. However, for many metal-organism combinations, data are lacking on the mechanism(s) of absorption, distribution, metabolism, and excretion, as well as mode of action. Improved understanding of these issues would improve linkages between exposure and effects or accumulation and effects.

It has, however, been established that, within certain limits, organisms either regulate their uptake of metal, store metals in forms not toxic to the organism (but potentially toxic to their consumers), or are efficient metal excretors. Which one of these strategies is employed may differ by metal and organism, particularly for those metals that are essential micronutrients. For example, for aquatic organisms that regulate uptake or excretion of a nonessential metal, tissue levels of metals are most frequently inversely related to water concentrations. Where the organism is effectively regulating internal levels of an essential metal, the amount in the organism can remain constant over a certain range of increasing environmental concentration. Under both scenarios, toxicity will occur only when some threshold is reached where the organism's regulatory mechanisms become overwhelmed. BAFs/BCFs should be derived using mathematical relationships that represent the concentration in the organism or tissue as a function of the concentration in the exposure medium/media (for BCF/BAF) for each set of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

exposure conditions. It is important to emphasize that these relationships should always be based on the environmentally available or bioaccessible fraction of the metal in those media (e.g., water column or sediment), to normalize the relationships for site-specific differences in environmental chemistry and associated metal speciation.

Furthermore, with many metal-organism combinations, the bioaccumulation process cannot be quantified with sufficient rigor to enable unambiguous predictions of metal residues in tissues that are toxicologically meaningful for evaluating impacts to aquatic organisms. Generally, the linkage between bioaccumulation as measured by whole body concentration and the potential for toxicological impact (i.e., the hazard), is lacking. In the case of direct toxic impacts, the *rates* of metal accumulation are generally more meaningful than tissue residues. Thus, the latest scientific data on bioaccumulation do not currently support the use of BCF and BAF data as generic threshold criteria for the acute or chronic hazard potential of metals. See Section 4.5.8 for further discussion.

Recommendations:

- BAFs/BCFs should not be used as indicators of acute or chronic metal toxicity. Aquatic organisms have regulatory mechanisms for actively excreting excess metal and/or for storing excess metal in detoxified forms which makes these relationships highly uncertain.

- Assessment of metal bioaccumulation should consider bioaccessibility, bioavailability, essentiality, acclimation/adaptation, regulation of metals (uptake and internal distribution), detoxification and storage as well as background accumulation. While the ability to quantitatively address all of these factors may be limited at the present time, their potential impacts should at least be qualitatively addressed..

- The latest scientific data on bioaccumulation do not currently support the use of BCF and BAF values when applied as generic threshold criteria for the hazard potential of inorganic metals (e.g., for classification as a “PBT” chemical).

- Because BCFs/BAFs of metals are influenced by organism background concentrations and metabolism or storage mechanisms, they should be expressed as a function of water concentration.

- The BCF/BAF derivation should also account for the concentrations and forms of the metal in the exposure media, to reflect speciation, bioaccessibility, and bioavailability as indicated. These BCF/BAF values should be limited to site-specific applications.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- First order kinetic (single-compartment models), pharmacokinetic (multi-compartment models) and biotic ligand models may also be useful for estimating bioaccumulation.

- Bioconcentration and bioaccumulation models should be developed using the bioaccessible/bioavailable form of the metal, to normalize for differences in environmental chemistry. Where data from the literature include only total metal in the environmental media, speciation models may be used to estimate this fraction. If such models are unavailable, the risk assessor should clearly state that use of such data increases the uncertainty of the risk characterization.

- For site-specific risk assessments, the preferred approach for assessing metal bioconcentration and bioaccumulation is through direct measurement from biota at the site.

- Metals become toxic when regulatory mechanisms are overwhelmed and the concentration at a site of toxic action exceeds a toxic threshold (known as critical body [or tissue] residues, CBRs). Because BCF/BAFs are dependent upon exposure concentrations, they should not be used as predictors of CBRs.

3.2.5. Trophic Transfer, Biomagnification, and Dietary Toxicity

Assessment of the potential impacts associated with trophic transfer of metals requires an understanding of the linkages between exposure and bioaccumulation in both the prey organism and the predator (or consumer) organisms. Organisms that bioaccumulate elevated levels of metals and make them available for consumer organisms are of concern. Examples include phytoplankton that can bioaccumulate some metals to several orders of magnitude above water concentrations; organisms that detoxify and store metals; and organisms that accumulate metals from sediments and, when consumed by aquatic animals, can translocate sediment-bound metals into aquatic food webs. However, biomagnification of inorganic forms of metals across multiple (i.e., three or more) trophic levels in aquatic food webs is considered rare. Biodilution can also occur for metals as Chen and Folt (2000) observed for As and Pb.

Notably, concentrations in both the predator and prey organisms can arise from multiple sources and uptake pathways (e.g., water as well as sediment), thus rendering field measures of metal body burdens an ambiguous measure of trophic transfer in these situations (which, by definition, reflects contaminant transfer from the diet only). Although the accumulated metal in a prey organism may serve as a source of exposure and toxicity to predator species, the presence of a significant metal burden in the prey does not necessarily mean that this metal is bioavailable to the predator. The bioavailability of accumulated metals in prey species to their predators can

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

vary significantly based on multiple factors, such as the form(s) of metal in tissues, the digestive physiology of the predator, and the tissues in which the metal is stored (e.g., exoskeleton vs. soft tissue). Development of analytical tools for quantifying the bioavailable fraction of accumulated metals to consumers (e.g., analysis of tissue fractions such as cytosolic metals) is currently an emerging area of research (e.g., Wallace and Luoma, 2003; Wallace et al., 2003). See Section 4.5.8 for further discussion.

Recommendations:

- Bioaccumulation and trophic transfer of metals does occur and can be an important source of exposure. In particular, consumers with high rates of metal uptake relative to elimination rates and high metal assimilation efficiencies are generally of greatest concern in aquatic food webs. However, biomagnification of inorganic forms of metals across three or more trophic levels in aquatic food webs is rare. Therefore, assessment of food web biomagnification alone is generally not an important aspect of classifying hazards or risks of inorganic metal compounds.

- Although the prediction of toxicity due to dietary exposure to inorganic metals is complicated by wide variation in the bioavailability and toxicity of accumulated metals, it is a factor that should be considered in metals assessments. Direct approaches to accomplish this include quantifying the bioavailable fraction of accumulated metals to consumers (e.g., analysis of tissue fractions such as cytosolic metals). Bioassay methods, such as feeding field-collected contaminated prey to predators under controlled conditions, offer another way to assess trophic transfer of metals, although such methods have not been widely standardized. These methods may be particularly useful for site-specific assessments, but they require knowledge of predator-prey relationships to be most applicable to field settings. Kinetic models also may be useful for predicting metal bioaccumulation in aquatic food webs (including trophic transfer); they show the most promise when applied and calibrated on a site-specific basis using experimentally derived kinetic parameters (e.g., uptake, assimilation, elimination, and growth dilution) that reflect typical environmental exposures. Efforts should continue to refine, evaluate, and apply models when warranted.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3.2.6. Sediment Exposure and Effects

Toxicity testing and benthic community assessments will continue to be important for evaluating exposure and effects of metals in sediments. Chemical-based approaches specific to evaluating metals in sediments have received increased attention. These include the simultaneously extracted metals-acid volatile solids (SEM-AVS) approach and use of interstitial pore water measurements. These approaches are focused primarily on estimating the toxicological potency (bioavailability) of metals in sediments to sediment-dwelling invertebrates. However, some uncertainties associated with estimating exposures to benthic invertebrates should be recognized. These include the creation of microenvironments by sediment organisms (e.g., irrigated burrows) and the influence of exposure through the diet sediment or metal-contaminated prey. For these reasons, the exposure pathway involving direct exposure to pore water is recognized as a simplification. Nevertheless, laboratory and field support exist for its application. See Section 4.5.10 for further discussion.

Recommendations:

- The SEM-AVS approach is the best available tool for screening analysis based solely on sediment chemistry. It is currently applicable to mixtures of copper, cadmium, zinc, lead, nickel, and silver.

- It is recommended that the use of SEM-AVS should be focused on identifying sediments where direct toxicity to benthos is *not* expected (i.e., SEM-AVS < 0); it is less powerful for predicting when toxicity will occur because it does not account for all factors that influence toxicity. A modification of the method is available to account for the presence of organic carbon within the sediment matrix.

- Consideration of uncertainties in the SEM-AVS approach include whether it is fully applicable to organisms living in microenvironments (e.g., irrigated burrows) or whether it adequately accounts for exposure via sediment ingestion. Some bioaccumulation of metal in benthic organisms may still occur when SEM-AVS < 0.

- The equalibrium partitioning (EqP) interstitial water approach may be combined with the SEM-AVS approach and direct measures of toxicity as part of multiple line-of-evidence approaches.

- The EqP interstitial water approach is best applied to identify nontoxic sediments; sediments that exceed this guideline may or may not show toxicity.

- The EqP interstitial water approach has been evaluated primarily for copper, cadmium, zinc, lead, nickel, and silver. Although the rationale may apply to other

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

metals and metalloids, supporting data should be sought before making this extrapolation.

- For oxic sediments, additional tools that may be used to relate metal lability/availability in sediments to toxicity include: pH-dependent partition coefficients of metals (generally linear over a range of interstitial water pH values); chemical, acid, and biomimetic extraction methods.

3.2.7. Metals Mixtures

Some of the recommendations given above apply to exposures and acute effects of select mixtures of metals in surface water or interstital pore water; methods for assessing chronic effects of mixtures are not widely developed. There are no realistic means to rank mixtures of metals or individual metals within mixtures. Recommendations follow on assessing risks of mixtures in aquatic environments. See Section 4.5.3 for further discussion.

Recommendations:

- The Concentration Addition Model is recommended for assessing acute toxic effects of mixtures with fewer than six components. In this approach, 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 using either Toxic Units (TUs) or Toxicity Equivalence Factors (TEFs) (for aquatic organisms, this can be accomplished through application of the BLM as a means of assessing binding of various metals to respiratory membranes). These calculations convert all metals to a single exposure/toxicity metric.

- The QICAR effects addition approach may be used to predict binary interactions of metals with joint independent action. The deviation from joint independent action can be predicted from the degree of similarity in binding tendencies for the paired metals.

3.3. METALS RISK ASSESSMENT RECOMMENDATIONS FOR TERRESTRIAL ECOSYSTEMS

As with any chemical, toxicity associated with metal exposures generally is estimated by using standard laboratory bioassays that are conducted in a manner similar to tests performed with organic substances. However, the response of organisms to metals is complicated by several factors that need not be considered for most organic substances. These include the natural background concentrations of the metals (including, but not limited to, the metal of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

interest) in either the test media or the site of concern, the acclimation of test animals to the culture conditions, whether or not the metal is an essential micronutrient, the potential interaction of the various metals, and the bioavailability of the metal. Recommended methods used to account for the influences of each of these factors that modify toxicity are presented here.

3.3.1. Fate and Transport

3.3.1.1. *Atmospheric Chemistry and Behavior*

With mercury being a notable exception, most metals and metal compounds occur primarily in the particle phase of the atmosphere. For purposes of risk assessment, the size of the particles is important. The aerodynamic size and associated composition of particles determines their behavior in the mammalian respiratory system, and particle size is one of the most important parameters in determining atmospheric lifetime of particles, as well as playing a role in associated deposition behavior. For those metals that may undergo transformation, much of the atmospheric chemistry takes place in the aqueous phase (e.g., cloud droplets or water films on particles).

Recommendation:

- Models to estimate metal speciation in atmospheric aquatic aerosols are of limited availability, with the use of the Community Multi-Scale Air Quality Model (CMAQ) for mercury being a notable exception. See Section 4.1.7. for further discussion.

3.3.1.2. *Soil Mobility*

Primary processes governing the environmental fate and transport of metals in the subsurface are advection, dispersion, matrix diffusion, and retardation (U.S. EPA, 1994a). Advection and dispersion are functions of the system rather than of the contaminant, so they are not specific to metals. Matrix diffusion, which is a function of the contaminant, is relatively unimportant and is omitted in most soil transport models. Retardation is contaminant and site specific. Because of this complexity, and the interactions between metals and environmental factors, proper characterization of soils is an important aspect of assessing and/or predicting the fate and transport of metals in terrestrial environments. Soil characteristics that can influence the fate and transport of metals include pH, the type and amount of organic matter (OM) in the soil matrix, soil particle size, soil compaction, and soil cohesiveness. Soil pH is among the most important properties to determine because it is considered the “master soil variable” that influences virtually all fate processes for metals in soil. These include solubility, precipitation,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

speciation, and sorption processes as well as microbial activity. See Section 4.4.1 for further discussion on soil transport models, and Section 4.4.1 for additional information on partition distribution coefficients (K_d).

Recommendations:

- A wide variety of analytical and chemical techniques may be used to characterize metal speciation. For particle-bound metals, direct measurement tools include x-ray absorption spectroscopy (XAS), x-ray diffraction (XRD), particle-induced x-ray emission (PIXE and μPIXE), electron probe microanalysis-scanning electron microscopy (EPMA-SEM), secondary ion mass spectrometry (SIMS), x-ray photoelectron spectroscopy (XPS), sequential extractions, and single-chemical extractions. See Section 4.1.8, Table 4-9, for further information about the applicability and limitations of each approach.

- Computer models may be used to predict speciation of metals in soil solutions. These include the Windermere Humus Aqueous Model (WHAM) (Tipping, 1998, 1994) and Non-Ideal Competitive Absorption (NICA) model (Gooddy et al., 1995). See Lumsdon and Evans (1995) for a good review of metal speciation models.

- 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 or to regional- and national-scale studies where bounds of potential K_d values, or reasonably representative single values are adequate.

- The MINTEQ model can be used to generate generic partition coefficients that may be applied to regional or national mobility evaluations (epa.gov/ceampubl/mmedia/minteq/index.htm or lwr.kth.se/english/OurSoftware/Vminteq/).

- Linearity of log K_d with pH may be assumed as a default approach for national-scale assessments. The value of log K_d for metal cation adsorption can be assumed to increase linearly with pH, whereas the value of log K_d generally decreases with pH for anion adsorption (Langmuir, 1997; Tessier, 1992). Partition coefficients tabulated as a function of pH are available and a useful way to proceed; non-pH-dependent values are available for lead (900), mercuric chloride (58,000), and elemental mercury (1,000) (U.S. EPA, 1999a).

- For higher level, site-specific assessments, metal adsorption may be estimated fairly accurately using literature information to estimate the sorption properties of metal oxides, clays, and OM, which are then used in diffuse layer sorption models. If greater accuracy or site specificity is required, it may be necessary to measure metal adsorption in laboratory experiments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- For site-specific assessments, K_d values developed for the site or for a similar location are generally preferred over generic or default values.

- If fluid flow in porous soil is isotropic and adsorption is fast, reversible, and linear, the Diffuse Layer (DL) model (also called the Generalized Two-Layer Model, or GTLM) in MINTEQA2 can be used to predict adsorption and precipitation behavior as a function of pH.

- PHREEQC, which has the DL metal adsorption model, can be used with the 3-Dimensional Flow, Heat and Solute Transport model (HST3D, a ground water flow and transport model), and the Chemical Transport (CHMTRNS) model also can be used to model metal transport through porous media.

3.3.1.3. *Transformation in Soils*

Methylation and demethylation of organic mercury compounds in soils are mediated by the same types of abiotic and microbial processes that occur in aquatic systems. Because soils are primarily oxygenated systems, particularly in the root zone, conditions favorable to sulfide formation and bacterial methylation occur infrequently. With the exception of peat bogs and similar anoxic, highly saturated soils, methylation generally occurs only at very low rates in soils. Plants also can transform metals and metalloids taken up from the soil. The most notable example is selenium. Soluble inorganic oxanions of selenium are readily taken up by plants and converted to organoselenium compounds, such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide.

The dissolution and transformation of a metal compound in soil is influenced by chemical and physical properties of the compound and of the soil. Environmental parameters, such as temperature and humidity, have a strong influence on the rate of transformation. 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. For example, insoluble forms of metals (e.g., vanadium pentoxide [V_2O_5]) will transform to soluble free ion (V) at a slower rate than will soluble metal salts (e.g., Na_3VO_4). However, it should be kept in mind that the rate of formation of the free ion is not proportional to the dissolution rate of the salt, as aging reactions that take place at the same time as transformation and dissolution will remove the free ion from the pore water. See Section 4.1.9 for further information.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Recommendations:

- In areas with well-oxygenated soils where methylation rates are very low, the mercury in soils and plants can generally be assumed to be an inorganic form.

- In lieu of site specific information, selenium in oxygenated soils should be assumed to be in the inorganic form.

- Selenium in plants and soil invertebrates should be considered as an organic compound for food chain analysis.

- Volatilization of all metalloids (mercury, selenium, arsenic) and organometallics should be considered when conducting detailed site-specific fate and transport models.

- Relative rates of dissolution and aging should be considered simultaneously to accurately predict pore water concentrations.

3.3.2. Exposure Assessment

Terrestrial wildlife, plants, and invertebrates accumulate metals from direct contact with soil or sediment, from ingestion of contaminated food (plants or other animals), and from incidental soil or sediment ingestion. Pathways of exposure include movement from soils through the food web and, to a lesser extent, air deposition either into soils or directly onto terrestrial receptors (e.g., plants). Because of significant differences in exposure patterns, it is convenient to discuss methods by receptor group (invertebrates, plants, wildlife) rather than by pathways or environmental compartments, with the exception of the contribution of natural background to total exposure, which is applicable to all organisms.

3.3.2.1. *Background*

EPA has provided detailed guidance on estimating background concentrations for site-specific assessments (U.S. EPA, 2002b, c, 2000c). Statewide average background soil concentrations are available in the U.S. EPA ecological soil screening levels (EcoSSLs) document (U.S. EPA, 2003c). Additional information on concentration of metals in soils at smaller spatial resolutions is provided in Shacklette and Boerngen (1984). Some metals (e.g., iron, copper, zinc) are included in the State Soil Geographic Database (STATSGO) available at www.nrcs.usda.gov/technial/techtools/ stat_browser.html. These data can be grouped at

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

whatever spatial scale is required, but they are not screened for whether they represent true background concentrations. See Section 4.5.4 for further information.

Recommendations:

- Use of a single number to represent background concentration for metals in all areas within the United States is of very little or no value owing to high variability across such a large geographic area.

- Averages (and ranges) of background concentrations for various ecoregions should be defined (Hargrove and Hoffman, 1999; Bailey, 1998; Omernick, 1986).

- If ecoregion-specific information is not available, a recommended default when conducting national-scale assessments is to use state averages.

- The range of background concentrations that might be encountered within the spatial scale being considered always should be defined.

- For a site-specific release of a highly bioavailable form of a metal, the background concentration may be a negligible contribution to ecological exposure and may be ignored in assessing ecological risk for that metal.

- For areas of contamination where added metals have aged significantly, reduced bioavailability should be considered. Thus, it becomes important to estimate exposure in terms of the bioavailable fraction.

- For site-specific risk assessments, it may not be necessary to consider background during the initial screen; bulk soil concentrations may be compared directly with derived toxicity thresholds for soil organisms.

- For metals that do not pass the initial screen (based on bulk soil measurements), adjustments for site specific bioavailability may be performed that will address the significantly lower bioavailability of contributions from background.

- Natural background levels should be taken into consideration during any remediation decisions because reducing soil metals below naturally occurring values will alter the plant and soil invertebrate community composition (potentially as dramatically as did the anthropogenically elevated soil levels).

3.3.2.2. *Soil Invertebrates and Plants*

The assessment of exposure and effects of metals on terrestrial plants and soil invertebrates should involve evaluating the bioavailability of the metals to the organism, the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

accumulation of metals in tissues, and the toxicity of the metals. The accumulation of metals in plants or soil invertebrates may be used as an indication of toxicity but also is a consideration when evaluating exposure to animals that feed on them. See Section 4.5.4 for further information.

Recommendations:

- Bulk soil concentrations collected in the top 0–12 cm of soil can be used as an initial estimate of exposure for soil organisms for all types of assessments.

- It is recommended that bulk soil concentrations be adjusted to account for bioavailability factors in higher level, definitive assessments; bioassays using site soils are encouraged for areas that do not meet initial screening level values.

- In higher level, definitive assessments, the organic matter on top of the soil (the "duff") should be analyzed separately to provide further detail on exposure to detritivores (such as *Collembola*) and deeper soil-dwelling organisms (e.g., various species of earthworms).

- Normalizing methods may also be useful for addressing soil variability in soil toxicity tests. Two normalizing metrics that have been used are percent organic matter and cation exchange capacity (CEC). Notably, it should be remembered that CEC is a function, at least in part, of soil pH. Therefore, normalization can be done only among soils of similar pH ranges.

- Most accurate estimates of exposures are generally achieved through measuring or modeling concentration of metals in soil pore water.

- Use of metalloregions for national-level assessments is encouraged to account for natural background levels and consequent adaptation of soil organisms.

- In characterizing risks to soil invertebrates and plants, it is important to recognize that soil concentrations below natural background may be harmful to native biota.

3.3.2.2.1. *Soil Invertebrates*

Ecological and anatomical differences among soil invertebrates influence exposure to and bioaccumulation of metals present in the soils. The soil ecosystem includes a complex food web of soil invertebrates (both hard- and soft-bodied invertebrates) that feed on each other, decaying plant material, and bacteria or fungi. For risk assessment purposes, however, exposure is typically described as a function of soil concentration rather than as a detailed analysis of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

movement of metals through the food web. Although this is a reasonable approximation for soft-bodied invertebrates (e.g., earthworms) whose exposure is primarily through soil pore water, there is more uncertainty in correlating soil concentrations with effects in hard-bodied invertebrates. These animals are exposed primarily through ingestion of food and incidental amounts of soil. Direct measurements, when possible, provide a means of ascertaining bioaccumulation for these hard-bodied species and can be used to judge the relationships between those residues and the bioavailable concentrations in soils and the tissue levels in soft-bodied animals such as earthworms. See Section 4.4.2.4.1 for further information.

Recommendations:

- For site-specific assessments, direct toxicity testing of the soil of concern often is the best method for assessing bioavailability and toxicity-to-soil biota (Fairbrother et al., 2002).

- Critical body residues (CBRs) provide an approach for judging the toxicity of metals to soil invertebrates based on tissue measurements. However, only a few CBRs have been developed for metals in soil invertebrates: cadmium and zinc in the springtail and cadmium in earthworms. See Section 4.5.9.2.

- For site-specific assessments, the concepts of pollution-induced community tolerance (PICT) may be useful for assessing effects on soil invertebrate communities. See Section 4.5.2.

3.3.2.2.2. *Plants*

Plants access metals through the pore water and have both active and passive mechanisms for taking up or excluding metals, depending on internal concentrations and whether 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 on rough cuticular surfaces that may provide an exposure route for herbivores. See Section 4.4.2.4.2 for further information.

Recommendations:

- The “soil-plant barrier” concept—developed for evaluating biosolids—influences the potential for bioaccumulation as well as toxicity. General assumptions that may be used include the following: strongly acidic soils (less than a pH of 4.5) increase plant uptake of zinc, cadmium, nickel, manganese, and cobalt and increase the potential for phytotoxicity from copper, zinc, and nickel; in alkaline soils, the high pH (greater

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

than 8) increases uptake of molybdenum and selenium; and lead and chromium are not absorbed by plants to any significant extent at any pH.

- The influence of soil chemistry on metal speciation should be considered when judging the potential for accumulation and/or toxicity to plants. Reduced soils can form sulfide, and sulfide forms low-solubility compounds for most metals, including lead, zinc, cadmium, copper, and nickel. For essential elements (e.g., zinc, copper, nickel), 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.

- Aerial deposition of metals onto leaf surfaces can be assumed inconsequential for plant exposure, with the exception of volatilized forms of metals, in particular mercury and lead.

- General categories of uptake based on bioavailability of metals to plants are shown in Section 4.

3.3.2.3. *Wildlife*

With some exceptions, risks of metals to wildlife species will typically involve estimating dietary exposures and relating these to Toxicity Reference Values (TRVs). For some vertebrates (e.g., especially amphibians), dermal exposures will be important. There also may be circumstances where inhalation exposures are important. Better understanding of when to consider dermal and inhalation pathways is needed. The recommendations given below emphasize the dietary route of exposure because this appears to be the most important pathway for most wildlife species and is better understood. This pathway includes food, water, and incidental soil or sediment ingestion. The relative importance of the dietary versus incidental soil ingestion pathways is dictated by (1) the degree to which food items are able to bioaccumulate metals from the soils, (2) the degree of incidental soil ingestion as a fraction of overall food intake, and (3) the relative bioavailability of the metal in the soil as compared to the metal in food items. See Sections 4.5.9 and 4.5.12 for further information.

Recommendations:

- Incidental ingestion of soil can be assumed to be an important route for exposure to wildlife when (1) the BAF from soil to food (e.g., to plants or soil invertebrates) is less than 1 and (2) the fraction of soil in the diet is greater than 5%.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- The same variables that restrict uptake by plants or other soil organisms can be assumed to reduce bioavailability to wildlife that ingest soil directly; an exception may be the lower pH that occurs in the digestive systems of many animals.

- Measured concentrations of metals in soil, surface water, and food items can be used in food chain models to estimate total exposure, or concentrations in food can be modeled using literature or site-specific bioaccumulation models. The recommendations given earlier for estimating bioaccumulation of metals in plants and invertebrates are applicable to estimating food concentrations for wildlife exposure models.

- Although bioaccumulation and trophic transfer of metals does occur, biomagnification (i.e., increases in concentration through the food web) is rare and may be assumed to be unimportant. Exceptions are the organometallic compounds, such as methyl mercury, that do exhibit biomagnification. It follows that with the exception of organometallic compounds, biomagnification is not an important consideration when evaluating the hazards of metals or when ranking metals based on hazard.

- CBRs reduce uncertainties because they account for site-specific bioavailability and multiple exposure pathways and should be used when available. However, very little information is available for metal CBRs in terrestrial wildlife; exceptions are methyl mercury, lead, selenium, and cadmium (Beyer et al., 1996). Tissue residues of other metals can be used to indicate that exposure is occurring but will not allow a determination of risk to be made.

3.3.2.4. *Food Chain Modeling*

Food chain modeling is used to estimate the exposure of wildlife to metals based on ingestion of soil, food, and water, and may also be useful in human health risk assessments. The basic format of the model is the same as that for organic substances. Detailed explanations are available in several related documents, such as U.S. EPA (2002h), (2003c), and (2004d). See also Sections 4.4.3 and 4.5.12 for additional information.

- EcoSSLs guidance – http://www.epa.gov/ecotox/ecossl/pdf/ecossl_guidance_chapters.pdf
- Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) – http://www.epa.gov/oppefed1/ecorisk/rra_chap_three.htm
- OAQPS Fate, Transport and Ecological Exposure Model (TRIM.FaTE) – http://www.epa.gov/ttn/fera/data/trim/tsdv2-sect7b-sept.pdf

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Recommendations:

- Measured or modeled concentrations of metals in soil, surface water, and food items may be used in food chain models. Available food chain models vary in their complexity (e.g., ranging from the use of soil-biota relationships and trophic transfer factors to bioenergetic models that simulate transfers of metals via inhalation and ingestion.)

- Information on diet, foraging area, similar topics is found in U.S. EPA (1993).

- In using wildlife exposure estimates to assess wildlife risk in screening assessments, relative (not absolute) bioavailability generally should be assumed to be either 1 (default value) or an appropriate site-specific estimate. However, very little information is available on dietary bioavailability for most wildlife species, particularly owing to differences in digestive physiology and anatomy across the board and the diverse range of mammalian and avian species. General guidelines are provided for some metals (e.g., lead) in NRC (1980), and values derived for human risk assessments (e.g., for lead) in U.S. EPA (2004) may be useful for animal species that have digestive systems similar to those of humans (generally omnivores); such information would be inappropriate for herbivorous animals. If data for one species (e.g., humans, cows, chickens) are used for another species, the uncertainties associated with animal to animal extrapolations for absorption of metals should be described.

- Food chain modeling should be used in national criteria-setting or hazard-ranking exercises. Screening level approaches and default values are detailed in the U.S. EPA EcoSSL documentation (U.S. EPA, 2003c).

- For site-specific risk assessments, it is recommended to begin with using default parameters and then successively adding more site-relevant data as particular species-exposure route combinations are not screened out; for methodology, see Fairbrother (2003).

3.3.2.5. *Bioaccumulation*

Characterization of metal bioaccumulation is an important component of many Agency assessments that range in complexity (i.e., from screening-level to definitive assessments) and overall scope (i.e., from to site-specific assessments to national ranking and characterization). Assessments may consider bioaccumulation either in terms of the potential for the metal to directly affect the organism and/or as the basis for estimating exposure to consumers via a trophic pathway. Understanding this component is relevant for ecological risk assessments, and also for human health assessments when the food chain pathway is involved.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The prevalence and importance of bioaccumulation in Agency assessments has brought increasing attention on the scientific validity and uncertainty of the methods used to characterize and quantify metal bioaccumulation. To reduce uncertainty in metals assessments, robust connections should be established 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. However, for many metal-organism combinations, data are lacking on the mechanism(s) of absorption, distribution, metabolism, and excretion, as well as mode of action. Improved understanding of these issues would improve linkages between exposure and effects or accumulation and effects.

It has, however, been established that, within certain limits, organisms either regulate their uptake of metal, store metals in forms not toxic to the organism (but potentially toxic to their consumers), or are efficient metal excretors. Which one of these strategies is employed may differ by metal and organism, particularly for those metals that are essential micronutrients. Where the organism is effectively regulating internal levels of an essential metal, the amount in the organism can remain constant over a certain range of increasing environmental concentration. Under this scenario, toxicity will occur only when some threshold is reached where the organism's regulatory mechanisms become overwhelmed. BAFs should be derived using mathematical relationships that represent the concentration in the organism or tissue as a function of the concentration in the exposure media (for BAF) for each set of exposure conditions. It is important to emphasize that these relationships should always be based on the environmentally available or bioaccessible fraction of the metal in those media (e.g., soil), to normalize the relationships for site-specific differences in environmental chemistry and associated metal speciation. See Section 4.4.3 for further information.

Furthermore, with many metal-organism combinations, the bioaccumulation process cannot be quantified with sufficient rigor to enable unambiguous predictions of metal residues in tissues that are toxicologically meaningful for evaluating impacts to soil organisms. Generally, the linkage between bioaccumulation as measured by whole body concentration and the potential for toxicological impact (i.e., the hazard), is lacking. In the case of direct toxic impacts, the *rates* of metal accumulation often are more meaningful than tissue residues. Thus, the latest scientific data on bioaccumulation do not currently support the use of BAF data as generic threshold criteria for the acute or chronic hazard potential of metals. See Section 4.5.6.3 for further information.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Recommendations:

- Measurements of metals in plant tissues, when possible, provide the most direct method for assessing bioaccumulation. When the data are to be used to evaluate exposure to higher trophic levels, measurements should be made of the appropriate edible tissues.

- Because BAFs of metals are influenced by organism background concentrations and metabolism or storage mechanisms, they should be expressed as a function of soil concentration.

- The BAF derivation should also account for the concentrations and forms of the metal in the exposure media, to reflect speciation, bioaccessibility, and bioavailability as indicated. These BAF values should be limited to site-specific applications.

- The latest scientific data on bioaccumulation do not currently support the use of BAF values when applied as generic threshold criteria for the hazard potential of inorganic metals (e.g., for classification as a "PBT" chemical).

- For national-level assessments, equations from Sample et al. (1999, 1998a, b) for uptake of metals from soil for soil invertebrates and for vermivorous wildlife (e.g., songbirds, voles, and shrews) and from Efroymson et al. (2001) for plant uptake may be used. However, the soil invertebrate models are not specific to soil type and therefore do not account for bioavailability factors such as pH, clay content, or cation exchange. Furthermore, they do not adequately predict chromium or nickel uptake.

- Soil parameter values from the 5th to 95th percentile of the area of concern should be used to bound the possible uptake rates (alternatively, Monte Carlo approaches can be used, assuming appropriate distributions for each parameter value).

- If using models for screening-level assessments, site-specific assessments may use measured soil parameter values. For detailed assessments, site-specific assessments may use either measured values of metals in soil organisms or site-specific bioassays to determine uptake rates (see Fairbrother, 2003).

- The highest accumulation of metals in plants occurs in the roots, and, except for hyperaccumulator species, most plant trophic transfer rates can be assumed to be <1.

- Plants are quite sensitive to some metals and may die before achieving levels high enough to be toxic to animals.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

3.3.3. Toxicity Assessment

Because metals are naturally occurring substances, toxicity assessment for ecological receptors exposed to metals requires an understanding of both the natural mechanisms for tolerance for (or, in the case of micronutrients, the use of) metals and the toxicological responses that occur when exposure exceeds the capacity of the organism to regulate its body burdens. Interactions between metals in either their uptake or toxicity (such as cadmium/calcium/zinc, mercury/selenium, copper/molybdenum) also should be considered in toxicity assessments. Risk assessments for metals are further complicated by the need to express the dose-response (or concentration-response) functions of bioavailable units that are functionally equivalent to measures of exposure. Issues of essentiality, appropriate toxicity tests, and acclimation or adaptation to continued exposures also should be considered.

3.3.3.1. *Adaptation and Acclimation*

Organisms have developed various mechanisms to cope with variable background metal concentrations, particularly for the metals that are essential elements. The genetic makeup of an organism defines its ability to cope with variable environmental conditions. The shifting of tolerance to a metal within the genetically defined limit of an organism is known as *acclimation* and generally involves physiological changes that may not always be passed on to offspring. Genetic *adaptation* results from increased survival of tolerant genotypes and subsequent changes in gene frequencies. Laboratory experiments conducted with F_1 generations obtained from metal-contaminated habitats provide the strongest evidence to support a genetic basis of tolerance (Klerks and Levinton, 1993), and new methods in toxicogenomics (e.g., microarrays) are providing additional insights. The ability of organisms to adapt or acclimate to metals in their environment should be considered when assessing chronic risks or determining the relative ranking hazards of metals. See Section 4.5.2 for further information.

Recommendations:

- For national-scale assessments, the country should be subdivided into metalloregions, such that protection levels, mitigation goals, and ranking results will be appropriate for the suite of species naturally present within each type of controlling environment.

- For site-specific assessments, the concepts of PICT can be applied.

- All reports of toxicity effects used in setting TRVs or benchmarks, whether for generally applicable national assessments or for site-specific assessments, should be

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

critically examined for information about how test organisms were raised and housed.

- For national-scale assessments, organisms should be acclimated to standard soils or (preferentially) to the various metalloregion soils.

- For site-specific assessments, acclimation should take place in soils with similar characteristics (e.g., percent clay, pH, OM, CEC) as the site of concern.

3.3.3.2. *Essentiality*

Essentiality is the requirement for metals in normal organism metabolic function. It is one of the primary factors that differentiates risk assessment for metals and metal compounds from that of synthetic organic chemicals and, therefore, requires specific consideration in risk assessments. Some trace elements, such as cobalt, copper, iron, manganese, selenium, molybdenum, and zinc, are necessary for the normal development of plants and animals. Other metals, such as arsenic, cadmium, lead, and mercury, have no known functions. Others may have beneficial metabolic effects but have not been shown to be essential. For essential elements, TRVs should not be below the optimal concentration range (or safe intake range). If set too low (i.e., in the range where deficiency can occur), the determination of risk will be erroneous and organisms actually may be harmed owing to lack of essential nutrients. See Section 4.5.1 for further information.

Recommendations:

- Metals that plants and wildlife require as micronutrients for normal organism metabolic function are identified in Table 4-14 in Section 4.5.1.

- Derived toxicity threshold values for essential elements should be used in screening-level risk assessments for both national and site-specific applications, if they are no more than 10-fold lower than the nutritional requirements. Otherwise, the required levels should be used as a threshold for allowable exposures. See Section 4.5.1.

- Higher level, definitive assessments may require additional bioassays to characterize the biphasic dose-response curve and determine both required and excessive threshold levels.

- For wildlife, the literature on dietary requirements of essential elements for livestock can be consulted. The National Research Council has published useful summaries (NRC, 1994, 1980), and a recent publication updates this information (McDowell, 2003).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Minimum concentrations required for plant growth are summarized in Epstein (1972, 1965) and Kabata-Pendias and Pendias (2001).

3.3.3.3. *Metals Mixtures*

Mixtures of metals (including metalloids and other contaminants) are commonly encountered in the natural environment as a result of anthropogenic inputs and the natural co-occurrence and enrichment of many metals. Interpretation of available information on the toxic effects of metal mixtures is complicated by differing measures and definitions of the bioavailable fraction of metals, whether it is the fraction that is available for uptake from the environment or at the site of toxic action. Two key questions should be addressed in risk assessments of metal mixtures: To what extent does each metal contribute to any observed effect? Are the effects significantly greater than or less than the sum of the individual component effects? See Section 4.5.3 for further information.

Recommendations:

- Metals that have the same mode of action initially can be assumed to be additive in effect.

- For metals with assumed additivity, either Concentration Addition or Effect Addition models can be used (see Section 4.5.3 for descriptions of these models).

- Effect Addition models, especially if based on body or tissue concentrations, are more accurate than Concentration Addition models but require reliable dose-response and bioaccumulation curves for all single metals and then careful testing of the models.

- National criteria for mixtures may not be possible because the combined effects depend on relative amounts of each metal and their relative bioavailability.

3.3.3.4. *Toxicity Testing*

Variability among soil toxicity test results is due in part to the influence of soil properties on bioavailablity of metals. Additionally, incorporation of sparingly soluble substances, such as many environmental forms of metals, into the soil matrix is difficult, and acclimation/adaptation of test organisms can further complicate test results. Use of soluble metal salts with the addition of organism to the test matrix immediately after mixing is not representative of most environmental situations, where aging and other physical/chemical processes affect metal

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

speciation and uptake. However, a large body of literature on the toxicity of metals to soil organisms and wildlife already has been developed. The risk assessor should use these data, taking into account the test-to-test variability in soil chemistry parameters and differences between laboratory test matrices and real-world conditions. See Section 4.5.11 for further information.

Recommendations:

- Existing toxicity data for soil organisms (plants and invertebrates) should be adjusted on the basis of OM, pH, and (if available) CEC to account for bioavailablity differences before use in any type of risk assessment or hazard ranking.

- Field data may be compared with laboratory toxicity response information by measuring metals in soil pore water from field assessments and comparing such data to spiked laboratory soils. This will increase the accuracy of the comparison by increasing the similarity of the bioavailability of the measured fraction.

- The effects of metals on plants can be evaluated by using either toxicity tests or published data. Toxicity tests performed by adding bioavailable metal salts to soils may provide different results than seen in field conditions with long-term metal exposures. The differences in bioavailability could be corrected by either allowing the added metals in the bioassays to age or by expressing metals in test soils in the environment as the bioavailable fractions (for protocols, see Fairbrother et al., 2002). Alternatively, measurement of metals in pore water from either field or laboratory studies will increase the comparability of results. The guidance provided for development of EcoSSL values (U.S. EPA, 2003c) is useful for judging the applicability of literature studies to plant toxicity threshold determinations.

- Sequential extractions of soil samples also may be used to estimate the bioavailable fraction. These treat soil samples with a succession of reagents intended to specifically dissolve different and less available phases of metals. Many of these techniques are a variation on the classical method of Tessier et al. (1979), in which metal associated with exchangeable, carbonate-bound, iron-manganese bound, organically bound, and residual species are determined. Although these methods are preferable to total metal extraction, relating the sequential fraction extracted to metal bioavailability is open to debate. For the application and limitations of extraction techniques, assessors should review Beckett (1989), Kheboian and Bauer (1987), and Foerstner (1987).

- Toxicity of metals to wildlife species can be expressed either as dose-response relationships or as TRVs; the latter have received the most application in risk assessments. Toxicity information is usually obtained from the literature because

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

case-specific toxicity studies are rarely done. The best sources of information on metal toxicity thresholds are NAS/NRC (1994, 1980), McDowell (2003), and the documentation supporting development of EcoSSL values (U.S. EPA, 2003c). The EcoSSL document also includes a general approach for screening studies for acceptability for use in derivation of TRVs for risk assessments. Uncertainty factors can be carefully applied if there is concern for extrapolation of data to species in a different taxonomic category (e.g., genus, family, class). General summaries for some metals are available in Beyer et al. (1996) and Fairbrother et al. (1996).

- Site-specific toxicity data can be developed for wildlife when the uncertainties associated with use of published data are large and the implications of the decisions warrant better information. These typically involve feeding studies with contaminated foods or soils contaminated with metals such as lead.

- Cross-species extrapolations should be conducted with some knowledge of animal physiology and specific responses to metals. Digestive physiology is the most important distinction because most metal exposures in wildlife are by the dietary route. However, other specific organismal responses should be understood as well. See Section 4.5.12.

- Use of critical tissue residues as an alternative approach to toxicity endpoints is conceptually sound but may requires significant research to establish critical tissue levels. Exceptions include some essential elements in plants, where deficiency/sufficiency concentrations in foliage have been developed, and tissue levels of lead, selenium, and cadmium in wildlife (Beyer et al., 1996). See Sections 4.5.6.3 and 4.5.12.

3.3.3.5. *Extrapolation of Effects*

Extrapolating the results of toxicity tests to untested species is necessary because of the paucity of data on the toxicity of metals to these receptors. However, extrapolation of results should be approached with caution owing to the large amount of uncertainty that can be introduced into the risk assessment process. Toxicological responses among species vary because of many physiological factors that influence the toxicokinetics (absorption, distribution, and elimination) and toxicodynamics (relative potency) of metals after exposure has occurred. These include (but are not limited to) differences in gut physiology, renal excretion rates, and egg production. Methods for extrapolating metal effects data among species are not unique to metals risk assessment. However, for metals, some species are able to regulate or store metals in their tissues without experiencing toxic effects (i.e., biota-specific detoxification), which makes extrapolations between species especially problematic. The essentiality of other metals adds

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

additional complexity to interspecific toxicity extrapolations. See Sections 4.5.11 and 4.5.12 for further information.

Recommendations:

- Methods for extrapolating toxicity thresholds among species (e.g., species sensitivity distributions (SSDs) are the same for metals as those used for organic substances and are subject to the same assumptions of physiological similarities and degree of required margin of safety (for a review of methods, see Kapustka et al., 2004).

- All extrapolations should account for different requirements for essential elements and the factors that modify metal toxicity (e.g., acclimation, essentiality, mixtures).

- SSDs should be used for extrapolating effects data among species (Van Straalen, 2001; Posthuma, 2001).

- A review of cross-species extrapolation methods can be found in U.S. EPA (2003).

- Across-metal extrapolations (even within the same species) should be avoided unless mechanisms of action are known to be similar.

- For soil invertebrates, extrapolating toxic response to one metal to potential effects of a nontested metal can be done using QICARS (Kapustka et al., 2004; Lewis et al., 2000).

- For plants and wildlife, there is sufficient information about modes of action of most common metals to make informed judgments about relative toxicity, so empirical extrapolation models such as QICARS would be applicable only for initial screens of minor elements.

- Caution should be exercised when using published or measured toxicity data to evaluate risks to plants in particular regions. This is because naturally occurring levels of metals play an important role in biogeographic distributions of plants and animals and may, in fact, be limiting factors in species distributions or use of landscapes. Thus, it becomes very important to define the geospatial location of the area to which the assessment results will apply.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4. METAL-SPECIFIC TOPICS AND METHODS

This chapter discusses metal-specific topics and methods to be used in the assessment of risk to humans and ecological entities from exposures to inorganic metals. It applies information and text from the metals issue papers and reflects contributions by EPA scientists and external experts. The final metals issue papers are available on the EPA Web site at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=86119.

Key topics and tools in this section are presented in subsections on environmental chemistry, exposure pathway analysis, human health effects, and ecological effects. The applications and limitations of the various models and methods for conducting metals assessments are presented to inform the reader. Topics and tools related to bioavailability and bioaccumulation are discussed throughout Chapter 4 because they have far reaching impact that crosses many aspects of metals assessment.

4.1. ENVIRONMENTAL CHEMISTRY

4.1.1. 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, it is necessary to understand the chemistry of the particular metal and the environment of concern. However, we can generalize factors that control metal chemistry and environmental characteristics where this generalization allows us to progress with estimates of metal fate and effects.

Metal speciation 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 and toxicity. The chapter then examines

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the occurrence and interactions of the metals of concern in natural media, including in surface and ground waters, soils and aquatic sediments, and the atmosphere. Important topics considered in these sections are metal sorption behavior, aging in soils, metal dissolution and transformation and transfer to plants, and methods of determining metal speciation in soils and sediments.

4.1.2. Hard and Soft Acids and Bases: The Stability of Complexes

Complexes are formed between metals (acids) and ligands (bases), both in solution and at the surfaces 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.

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. Strong, relatively covalent bonds are formed in complexes between soft and borderline soft acid cations and soft bases. Ligand binding sites on the external or internal surfaces of organisms are often of soft base character and thus bond strongly with soft and borderline soft acid cations.

A useful concept that helps to explain the strength of metal complexing and metal toxicity is that of hard and soft acids and bases (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 4-1 summarizes hard and soft acid and base relationships for the metals of concern. The first text box summarizes the applicability of hard and soft concepts to the formation of metal complexes; the second text box defines ligands.

Ligands

Ligands are anions or molecules that form 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Hard metals (hard acids), which are the least toxic, preferentially bind with hard bases that contain oxygen, forming weaker bonds with soft nitrogen and sulphur 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

Table 4-1. 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^{-}, $C_2O_4^{2-}$, CrO_4^{2-}, MoO_4^{2-} $H_nPO_4^{n-3}$, $H_nAsO_4^{n-3}$, 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-}, $H_nAsO_3^{n-3}$, $C_6H_5NH_2$, C_5H_5N, N_3-, N_2
Soft bases	I^{-}, HS^{-}, S^{2-}, CN^{-}, SCN^{-}, Se^{2-}, $S_2O_3^{2-}$, -SH, $-SCH_3$, $-NH_2$, R-, C_2H_4, C_6H_6, RNC, CO, R_3P, $(RO)_3P$, R_3As, R_2S, RSH, RS^{-}

Source: Modified after Huheey et al. (1993) and Langmuir (1997). "R" refers to an organic molecule.

sulfide, generally in the following order: $Pb^{2+} > Cu^{2+} > Cd^{2+} > Co^{2+} \cong Fe^{2+} > Ni^{2+} > Zn^{2+} > Mn^{2+}$. The tendency of metals to bind to soft ligands or to organic substrates (which are usually soft) is greatest for soft and borderline metals (soft acids), followed by the hard metals (hard acids), typically in the order $Pb^{2+} > Cu^{2+} > Cd^{2+} > Zn^{2+} > Ca^{2+} > Mg^{2+} >> Na^{+}$ (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+} ($\log K_{sp} = -57.25$) or Ag^{+} ($\log K_{sp} = -49.7$), whereas borderline hard and hard metal cations such as Mn^{2+} ($\log K_{sp} = -19.25$) or Fe^{2+} ($\log K_{sp} = -22.39$) form slightly more soluble, although still highly insoluble, metal sulfides.[1] These

[1]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).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

differences in solubilities are fundamental to the method of acid-volatile sulfide (AVS) normalization of sediment-associated metals (see Section 4.1.5, on Sediment Chemistry). Finally, according to the Biotic Ligand Model (BLM) (see Sections 3.1.4.2 and 3.4), effects of metals are related to or correlated with metal interactions with biological ligands, which are generally soft base species.

4.1.3. Aquatic Chemistry

4.1.3.1. *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:

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

where the terms γ_{Pb} and γ_{SO4} are the activity coefficients of the ions. The product of the ion activity coefficient and the molal concentration of each species equals the activity of the ion. This equation shows that the activity of free lead ion controls the solubility of lead sulfate. For a given total lead concentration (see the previous equation), the more of the lead that is complexed, the lower will be the concentration of free lead ion. This means that as the extent of lead complexing increases, the total lead concentration must also increase to reach saturation with lead sulfate. In other words, metal complexing increases total metal solubility.

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

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 assumes that the free or aquo-ion is the most biologically active form of the dissolved metal. Accordingly, the key parameters that can modify the degree of toxicity are those that affect speciation, such as pH and the amount of inorganic and organic ligands (e.g., dissolved organic carbon, DOC) that can form metal complexes and so provide alternative binding sites for the metal ion. Metal toxicity is also affected by other dissolved ions (e.g., Na, Ca) that compete with metals for binding sites on the gills of fish or on respiratory surfaces of other aquatic organisms.

4.1.3.2. *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 4.1.4, 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 and decreases with increasing pH.

Figure 4-1 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 dissolved organic carbon (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).

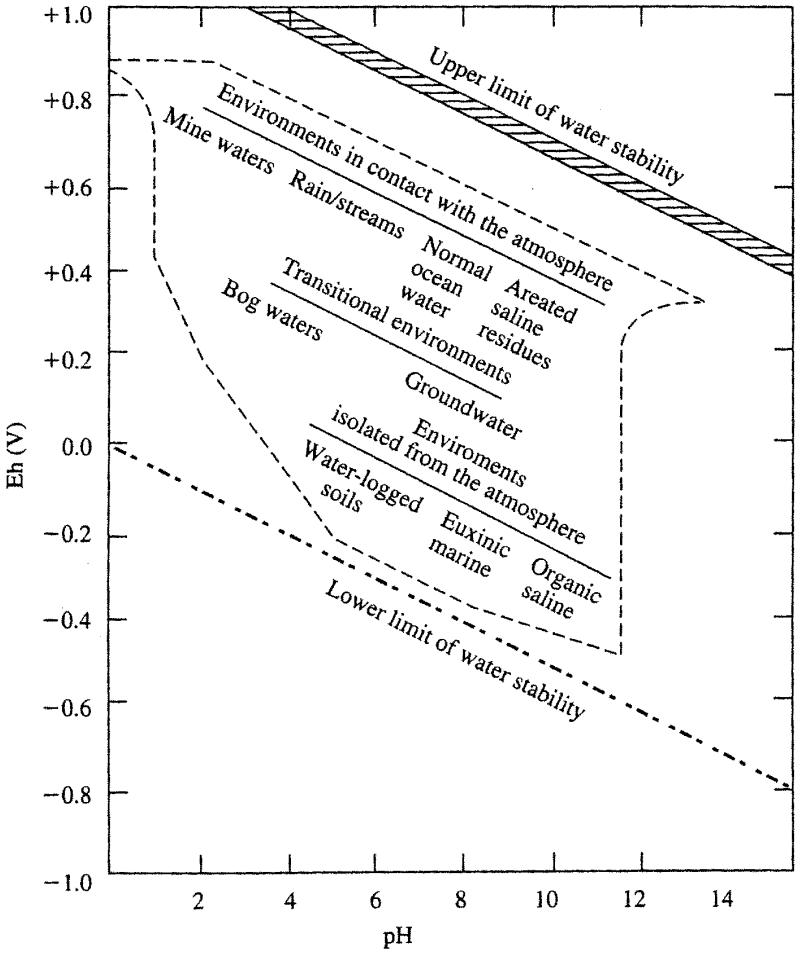

Figure 4-1. Approximate positions of some natural environments in terms of Eh and pH. The dashed line represents the limits of measurements in natural environments, as reported by Baas-Becking et al. (1960).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Microorganisms play an essential role in defining the redox conditions in aquatic systems. The effect of the common sequence of microbially mediated redox reactions on Eh when conditions in a water or sediment become more reducing (depleted in oxygen) or oxidizing is shown in Figure 4-2. These reactions importantly affect or are affected by the redox behavior of the major elements C, S, N, Fe, and Mn and also affect the mobility of most of the metals of concern, which have multiple redox states (Sb, As, Cr, Co, Cu, Mn, Hg, Mo, Ni, Se, and Ag). Thus, Cr(VI) (oxidized) in chromate ion is highly mobile in aqueous environments compared to Cr(III) (reduced). Cr(VI) is considered a known human inhalation carcinogen, whereas Cr(III) is generally considered to have low human toxicity. Among the microbially mediated reactions in Figure 4-2, the one that most affects possible metal toxicity is sulfate reduction, which requires the presence of organic matter. Sulfate reduction produces hydrogen sulfide, which reacts with

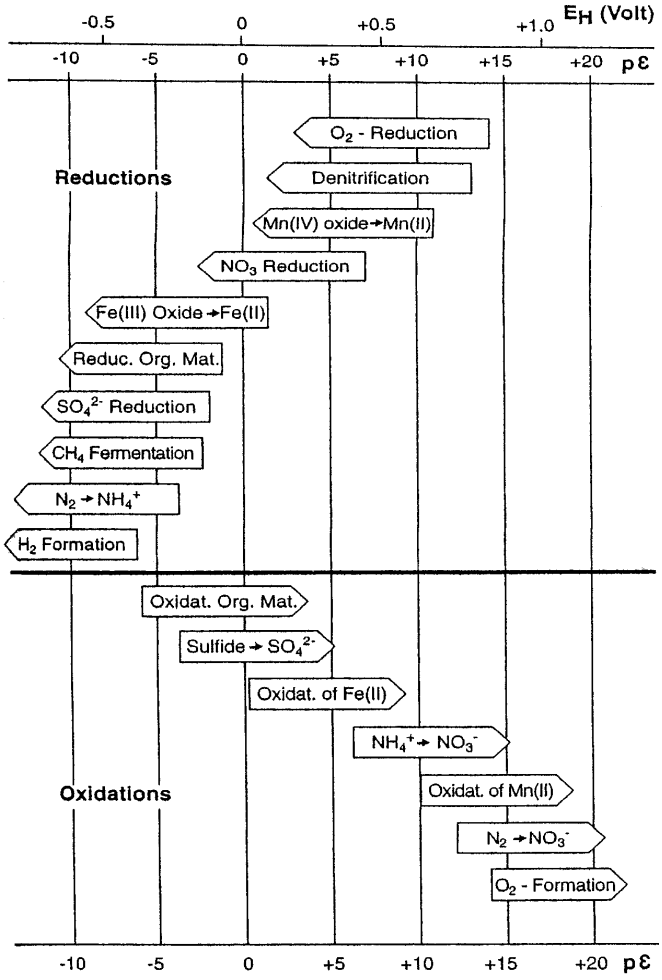

Figure 4-2. Sequence of microbially mediated oxidation-reduction reactions.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

metals such as Sb, As, Cd, Co, Cu, Pb, Hg, Mo, Ni, and Ag and can cause their almost quantitative precipitation as insoluble metal sulfides. This immobilizes these metals and so makes them unavailable to plants and animals.

Much of the preceding discussion of the importance of metal speciation, hard and soft acids and bases, oxidation potential, and metal sulfides, is summarized in Table 4-2. The table shows, for example, that the hard acid metals Al, Ba, Be, and Sr have but one oxidation state and do not form insoluble sulfides; thus, their solubilities and mobilities are not directly affected by redox conditions, although they are strongly affected by changes in pH. Also indicated are forms of the metals that occur in soils and waters, with As, Mo, Se, and sometimes Cr and V occurring as oxyanions, and most of the other metals occurring usually as metal cations. Eh-pH diagrams for the redox-sensitive metals of concern and of major elements such as Fe, S, and C are given in Langmuir et al. (2004). These show the detailed occurrence of the metal species under oxidizing and reducing conditions. In simplified terms, the Eh-pH diagram and Table 4-2 show that Fe, Mn, and Tl are most mobile under reducing conditions, whereas S and the remaining metals of concern are usually most mobile under oxidizing conditions.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-2. Important properties of trace metals as they occur in natural waters and mineral systems: oxidation states, redox sensitivity, tendency to form sulfides at low Eh, dominant chemical species of metals in soils and natural waters not considering most (especially weak) metal complexes

Metal	Symbol	Hard or soft	Oxidation states	Oxidized forms	Reduced forms[a]	Can form sulfides at low Eh	Soils	Waters
Aluminum	Al	H	3+	Al^{3+}	Al^{3+}	no		
Antimony	Sb	H/S	5+, 3+, 0	$Sb(OH)_6^-$	$Sb(OH)_3^o$/Sb(s)	yes	$Sb_{III}O_x$?	$Sb(OH)_6^-$
Arsenic	As	H/S[b]	5+, 3+, 0	$HAsO_4^{2-}$	$H_3AsO_3^o$/As(s)	yes	AsO_4^{3-}	AsO_4^{3-}, AsO_3^{3-}
Barium	Ba	H	2+	Ba^{2+}	Ba^{2+}	no	Ba^{2+}	Ba^{2+}
Beryllium	Be	H	2+	Be^{2+}	Be^{2+}	no	Be^{2+}, $Be_xO_y^{2x-2y}$	Be^{2+}
Cadmium	Cd	S	2+	Cd^{2+}	Cd^{2+}	yes	Cd^{2+}	Cd^{2+}
Chromium	Cr	H	6+, 3+	CrO_4^{2-}	Cr^{3+}, $Cr(OH)_3$(s)	no	Cr^{3+}	CrO_4^{2-}, Cr^{3+}
Cobalt	Co	B	(3+), 2+	(Co^{3+}), Co^{2+}	Co^{2+}	yes	Co^{2+}	Co^{2+}
Copper	Cu[a]	B/S[b]	2+, 1+, 0	Cu^{2+}	Cu^+/Cu(s)	yes	Cu^{2+}, Cu-OM[b]	Cu^{2+}, -fulvate
Lead	Pb	B	(4+), 2+	Pb^{2+}	Pb^{2+}	yes	Pb^{2+}	$Pb(OH)^+$
Manganese	Mn	H	(4+), (3+), 2+	(4+), 2+	(3+), 2+	no[b]	Mn^{4+}, Mn^{2+}	Mn^{2+}
Mercury	Hg	S	2+, 1+, 0	Hg^{2+}	Hg^+/Hg(l)	yes	Hg^{2+}, CH_3Hg	$Hg(OH)_2^o$, $HgCl_2^o$
Molybdenum	Mo	H/S	6+, (5.33+), 5+, (4+)	$HMoO_4^-$	MoO_2^+/Mo_3O_8(s)/MoS_2(s)	yes	MoO_4^{2-}	MoO_4^{2-}
Nickel	Ni	B	(3+), 2+	(Ni^{3+}), Ni^{2+}	Ni^{2+}	yes	Ni^{2+}	Ni^{2+}
Selenium	Se	H/S	6+, 4+, (0), 2-	SeO_4^{2-}	SeO_3^{2-}/Se(s)/HSe^-	no	SeO_4^{2-}, $HSeO_3$	SeO_4^{2-}
Silver	Ag	S	1+, (0)	Ag^+	Ag^+/Ag(s)	yes	Ag^+	Ag^+, AgCl
Strontium	Sr	H	2+	Sr^{2+}	Sr^{2+}	no		
Thallium	Tl	S	(4+), (3+), 1+	(Tl^{4+}), (Tl^{3+})	Tl_2O(s)/Tl^+	yes		
Vanadium	V	H	5+, 4+, 3+	$H_2VO_4^-$	VO^{2+}, $V(OH)_3^o$	no	$V_{IV}O_x$?	HVO_4^{2-}
Zinc	Zn	B	2+	Zn^{2+}	Zn^{2+}	yes	Zn^{2+}	Zn^{2+}

Oxidation states in parentheses are found in mineral systems only. Hard (H), soft (S), and borderline soft (B) metals are indicated.

[a] Cu^{2+} is bordeline soft, and Cu+ is a soft cation. Typically, much or most of Cu in soils is complexed with organic matter.

[b] B/S or H/S denotes whether the oxidized species is borderline hard or hard, and the reduced species is soft.

[c] Cu-OM denotes copper complexed with organic matter.

Source: Modified after Logan and Traina, 1993.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.1.3.3. *Effects Concentration and Bioavailability*

The traditional method of predicting effects of metals on aquatic organisms is to estimate an effects concentration for the water column and the sediment. For the water column, the EPA's Water Quality Criteria (WQC) (U.S. EPA, 1996a; Stephen et al., 1985) or the Predicted No-Effect Concentration (PNEC) derived following the European Union's (EU's) technical guidelines (EU, 1996) are frequently used as default screening values. However, these criteria make only limited corrections for bioavailability, taking into account only water hardness and ignoring other modifying factors such as pH and competing ligands. The BLM was developed to remedy this situation (Paquin et al., 2002a; U.S. EPA, 2000d; Di Toro et al., 2000). It incorporates the WHAM speciation model and it also models the competitive metal binding at the toxic site of action (the biotic ligand). BLMs are currently available for copper and silver (Di Toro et al., 2000; Santore et al., 2000) and zinc (Santore et al., 2002) and are under development for cadmium, nickel, and lead (see www.epa.gov/waterscience). The development and use of the BLM is covered in detail in Section 4.5, Characterization of Ecological Effects.

4.1.4. Ground Water and Metals Mobility

Site-specific risk assessments for EPA programs often need 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, 1994c). 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, 1994c) 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.

- **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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

4.1.4.1. *Metals Sorption*

4.1.4.1.1. ***Introduction.*** The ability of a trace or minor metal such as a metal of concern to sorb to a substrate is usually the determining factor in its mobility. Physical adsorption, which is important for molecular organic compounds, is largely inapplicable to the sorption of the trace metals, which are usually adsorbed as ionic species. In fact, trace metal adsorption is ofen relatively independent of the concentrations of the major ions. *Trace metal adsorption is strongly pH-dependent and a function of ionic strength, metal complex formation, competitive ion sorption, redox conditions, and the amounts and reactive surface areas of specific sorbing solids.* The most accurate and mechanistic approach to modeling and predicting trace metal adsorption is *surface complexation modeling*, using a model such as the *Diffuse Layer (DL) model*, which ideally can account for all of these variables (Langmuir, 1997; Stumm and Morgan, 1996).

The degree of mobility of organic contaminants is often expressed by means of a single *partition coefficient* (K_d) value that describes the distribution of a species between sorbed and dissolved forms (U.S. EPA, 1995a). Mobility is then calculated from the partition coefficient. Such an approach is applicable to metal adsorption only when the conditions listed above are practically constant and are the same in the environment as in the laboratory where the K_d was determined, which is rarely the case. In fact, when metal adsorption is described using partition coefficients, the value of such coefficients typically should be varied by two or more orders of magnitude to reproduce metal adsorption behavior at a specific site. Therefore, single partition coefficients for metals are of little value except in broad regional surveys when a large uncertainty in a K_d value may be acceptable.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

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

It may be possible to estimate metal adsorption with acceptable accuracy without having to measure it, depending on the information available on a specific soil, surface water, or ground water system. What is needed minimally is the weight and surface area of potentially sorbing materials (e.g., metal oxides, clays, and organic matter) in a volume of soil or sediment, or in suspension in a stream. Literature information can then be used to estimate the sorption properties of these materials for use in a sorption model. For example, as noted above in the discussion of the DL adsorption model, where HFO is the dominant sorbent and the amount suspended in a stream is known, estimation of metal adsorption can be accurate to within 10–20%, as shown in Table 4-3 (Smith et al., 1998). As a general observation, other factors being equal, it has be found that the surface charge density—and thus the metal adsorption capacity—of most minerals is largely a function of their surface areas exposed to water (Pabalan et al., 1998). Thus, the adsorption of metals by Al and Fe(III) oxyhydroxides in a system at a given pH may be assumed to be the same if they have the same surface areas.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-3. Comparison of model predictions[a] and measured values of percent metals associated with the suspended particulate fraction of mine drainage waters from select sites

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

[a]Model predictions made with the Diffuse Layer model and MINTEQA2.
[b]Dissolved concentration was below the detection limit; value was computed using the limit of detection for the dissolved concentration.

Source: Smith et al., 1998.

Cederberg et al. (1985) and Yeh and Tripathi (1991) considered surface complexation modeling of metal adsorption and metal transport in ground water. Parkhurst (2002) developed a computer model called PHAST,[2] which is a three-dimensional reactive transport model that combines PHREEQC, which has the DL metal adsorption model, with HST3D, a ground water flow and transport model.

Several recent studies have measured and modeled trace metal adsorption and metal transport in streams using a surface complexation approach to adsorption. U.S. Geological Survey researchers of the Toxic Substances Hydrology Program have published a number of papers using the OTEQ and OTIS models. OTEQ is a one-dimensional model for studying the fate and transport of metals in streams and rivers. The model couples the OTIS transient storage model with MINTEQ, which includes DL model adsorption of metals by HFO (Ball et al., 1999; Runkel et al., 1999). Runkel et al. (1999) considered in-stream metal transport, metal oxide precipitation-dissolution, and pH-dependent sorption of copper and zinc.

If greater accuracy or site specificity is required, it may be necessary to measure metal adsorption in laboratory experiments. Such measurements can be performed on pure minerals or on whole (usually sieved) soils. The sorption results may be used to develop DL model

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

parameters for metal adsorption (Stumm, 1992; Dzombak and Morel, 1990). For example, model results may then be used to compute partition or distribution coefficients as a function of pH.

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

4.1.4.1.3. ***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:

$$R_f = \frac{\nu_p}{\nu_c}$$

where R_f is the retardation factor,
ν_p is the velocity of water through a control volume, and
ν_c is the velocity of contaminant through a control volume.

The retardation factor is related to the distribution coefficient through the expression:

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

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

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:

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The properties and applications of partition or distribution coefficients for metals are comprehensively reviewed in U.S. EPA (1999a). These coefficients may be obtained from the literature, estimated using mathematical models, or measured. In batch tests, vessels are filled with a known amount of sorbent solid mixed with a known volume and concentration of a sorbing metal species (the sorbate). Often the approach is to systematically vary sorbent or sorbate concentrations and pH is a series of centrifuge tubes, for example. After centrifugation, the amount of sorbed concentration is determined by difference from the total sorbate added. The value of K_d, usually in mL/g, is then computed from the expression:

$$K_d = (\text{wt. adsorbed} / \text{wt. sorbent}) / \text{solute concentration}$$

In column test experiments, K_d may be computed from test results with the expression:

$$K_d = [(C_i - C_f)V] / C_f * M]$$

where C_i and C_f are the initial and final concentrations of sorbate,
V is the volume of soln passed through the column, and
M is the mass of solids in the column.

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

Retardation coefficients tabulated as a function of pH by EPA (U.S. EPA, 1998a) are listed in Table 4-4 for several important metals of potential concern. EPA (U.S. EPA, 1999b) has also presented non-pH-dependent values for lead (900), mercuric chloride (58,000), and elemental mercury (1,000), which for reasons just discussed should be used with considerable caution.

Values for Lead

Values for lead are not tabulated because of their large variability and the difficulty of selecting values that would be representative or meaningful.

4.1.4.1.4. ***Limitations.*** The use of single K_d values for a given pH contains potentially large errors. The values in Table 4-4 will apply only to a specific sorbing phase, amount of sorbent and its reactive surface area, solution-to-solid ratio, and water chemistry. For example, on a weight basis, clays are far less sorbing for most metals than are the FHO or OM. Single K_d

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

values should be limited to regional studies and should be adjusted to account for regional variations in soil properties.

Table 4-4. Partition coefficients as a function of pH for several important elements of potential concern

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

Source: U.S. EPA (1998b).

The distribution coefficient approach may apply if fluid flow in the porous media (soil or sediment) is isotropic and adsorption is fast, reversible, and linear (Freeze and Cherry, 1979). These assumptions are often not valid for metal adsorption. Some transport models assume a constant partition coefficient or linearity of the partition coefficient over all concentration ranges. To the extent that sorption is not constant and follows a nonlinear isotherm (which is the usual case for metals), these models will be inaccurate. The best that can be hoped for when single partition coefficients are used to describe metal adsorption is that they represent bounding values in a given application.

4.1.4.1.5. ***Use in decision making.*** U.S. 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(http://www.epa.gov/ceampubl/mmedia/ minteq/index.htm or http://www.lwr.kth.se/english/ OurSoftware/Vminteq/).

For screening assessments:

- 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 lead (900), mercuric chloride (58,000), and elemental mercury (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, depending on the information available on a specific soil, surface water, or ground water system. What is needed minimally is the amounts and surface areas of the potentially sorbing materials (e.g., metal oxides, clays, and 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 DL sorption model, for example.

- 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 experiments could be batch tests that attempt to reproduce the composition of waters and sorbing solids in the study area.

4.1.5. Sediment Chemistry

In addition to the challenges posed by metal chemistry, the sedimentary environment is complex and often highly heterogeneous. Fortunately, we can generalize about the sedimentary environment and the main controlling factors 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 proportions of a chemical held by sediment relative to water is a function of a

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

metal's chemistry as well as the chemistry of the sediment solid and the surrounding environment, and this distribution is dynamic (Diamond and Mudroch, 1990). Because of their large capacity to "hold" metals, sediments have been characterized as "sinks." Although this is largely true, sediments are now appreciated to be temporary sinks, wherein some of the metal can enter ecological and human food webs through several routes (e.g., Diamond, 1995), primarily through accumulation in benthic organisms. These organisms include those that fully or partially live in the sediments (e.g., tubificids, chironomids, trichopteran larvae) or those that feed from the sediment bed (e.g., suckers, carp). Some organisms obtain their chemical dose from both pelagic and benthic routes (e.g., lake whitefish, walleye), but because of high chemical concentrations in sediments, the benthic route can be the dominant route of uptake (Morrison et al., 2000).

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, fine-grained particles are of greatest significance in terms of metal binding.

For humans, the route of entry of metals from the sediments is through water used for drinking, bathing, and swimming. The availability of these metals is mediated by sediment-water exchange processes that can result in the release or remobilization of chemicals from the sediment bed. However, due to the ability of Hg to bioaccumulate in its monomethyl form, fish consumption is the critical route of exposure to this metal for humans.[3]

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 the sediments will reveal decreasing sediment porosity and concentrations of dissolved oxygen because oxygen is consumed as organic matter decomposes. pH is often relatively constant or may decrease with depth, but alkalinity may increase 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.

[3]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).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The sequence of microbially mediated redox reactions that produce these reduced species are given in Figure 4-2.

The redox status of the sediments can be assessed 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 redoxycline, which can migrate vertically, depending on the mixing of the overlying water column (e.g., Diamond and Mudroch, 1990). For example, the redoxycline may be 5 to 10 cm below the sediment-water interface in a well-oxygenated oligotrophic lake or river, but it may be above the sediment-water interface in a thermally stratified eutrophic lake or river.

4.1.5.1. *Metal Chemistry in Sediments*

In this discussion, two pools of metals should be considered. The first pool consist 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, we will consider only the exchangeable pool of metals. Note that the exchangeable pool will be composed of naturally occurring metals that are released into solution due to weathering and diagenetic processes as well as metals released into the environment due to anthropogenic activities.

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

The concentration of metal in the dissolved phase is controlled by sorption to the solid phase. 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 we neglect the kinetic limitation of reactions, the distribution of metals

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

among aqueous species and between the aqueous phase and the solid phase can be estimated. 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 redoxycline moves more quickly than the rate of metal reaction or when the reaction is governed by microbial processes, as occurs with the methylation of mercury or arsenic.

In oxic sediment pore waters (above the redoxycline), metals will exist as aqueous species, that is, as freely dissolved ions 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 sulfur 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 AVSs in regulating toxicity).

As a result of redox chemistry, metals can undergo seasonal redox-driven cycling between the water column and sediments or within the sediments, depending on the position of the redoxycline. The stages in the cycling are, first, the 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

solid-phase sediment profile reflects this reworking rather than the historical record of metal loadings (MacDonald et al., 2000).

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 arsenic, that exist as anionic species.

4.1.5.2. *Methods of Estimating Metal Distribution in Sediments*

4.1.5.2.1. ***Application.*** A main objective in terms of assessing the hazard or risk posed by metals is estimating metal in the dissolved phase that is potentially bioavailable. Accordingly, several methods have been developed to estimate the distribution of metals among dissolved and solid phases in sediments. These methods have been thoroughly reviewed by Mudroch et al. (1999, 1997). Although bioavailability is also a function of aqueous phase speciation (see Section 4.1.3, Aquatic Chemistry), limited research has been conducted to estimate metal speciation in pore waters. Generally, ecological risk assessments assume that the exposure of benthic organisms to sediment-associated metal is proportional to the metal concentrations in interstitial water, although some studies indicate that uptake from overlying water (Hare et al., 2003; Roy and Hare, 1999) or ingested sediment may be a significant source of body burdens of metals (see Section 3.2, Metals Risk Assessment Recommendations for Aquatic Environments, for more discussion of this topic).

Distribution of metals in sediment pore waters may be determined by field measurements, experimental methods, and mathematical modeling, with the latter also requiring some field measurements. Concentrations of metals in pore waters may be determined in the field by use of pore water dialysis chambers or peepers and by methods that separate the solid phase from the pore water, although the latter have been shown to be less reliable (Mudroch et al., 1997). Several extraction schemes have been developed to determine the distribution of metal among operationally defined fractions (e.g., Forstner, 1995a; Tessier et al., 1979). It is well known that sequential extraction methods do not cleanly distinguish the occurrence and speciation of different forms of metals in sediments and soils (Tye et al., 2003; Verloo, 1999). Other experimental methods include leaching tests (e.g., Reuther, 1999). The results of any of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

these methods are concentrations of metals in pore water, which can be related to toxicity benchmarks.

Because of the need to develop Sediment Quality Guidelines (SQGs) for metals that explicitly address toxicity and are based on readily measured parameters, several methods have been developed. For oxic sediments, Tessier and co-workers (Tessier 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 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.

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, 1995a). Studies have demonstrated an inverse relationship between sediment 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 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 4.5.

For estimating effects concentrations in the sediment, there are many different SQGs, which vary in their derivation and the degree to which they incorporate bioavailability considerations. Many of the published SQGs are based on empirical relationships between biological effects and the total (dry weight) concentrations of sediment contaminants (e.g., McDonald et al., 1996; Long and Morgan, 1991). Although these empirically based guidelines do show general relationships between the degree of sediment contamination, they do not explicitly account for site-specific differences in bioavailability of contaminants. Although EPA has not formally adopted any single SQG approach as an Agency standard, it has been active in developing the “equilibrium partitioning” (EqP) approach to SQG development. The EqP

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

approach considers effects of sediment chemistry on bioavailability by comparing the concentrations of AVSs, SEM, and organic carbon (U.S. EPA, 2000c; Ankley et al., 1996, 1993; Di Toro et al., 1992, 1990). This approach is reviewed in more detail in Section 4.5, Characterization of Ecological Effects.

4.1.5.2.2. ***Limitations.*** 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.

4.1.6. Soil Chemistry

The cationic metals occur naturally in soils as oxides and hydroxides (Fe, Mn, Al); to a lesser extent 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, anions, or neutral species. 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).

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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).

4.1.6.1. *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 Fe and Al 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).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.1.6.2. *Adsorption Behavior of the Metals of Concern*

4.1.6.2.1. ***Surface area and surface density.*** In porous media, the most important sorbent solids for metals are oxyhydroxides of Fe and Mn. 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.

4.1.6.2.2. ***Importance of pH.*** The pH at which a solid surface changes sign is referred to as the zero point of charge (ZPC). The ZPC of organic matter and kaolinite are below the range of usual pH and while their surface charge decreases with decreasing pH, their surfaces remain negatively charged above pH 2–3. In contrast, Fe(III) and Al oxyhydroxides, such as goethite (α-FeOOH), have ZPC values near pH 7–8 and so have a positive surface charge at low pH and a negative surface charge at high pH. Thus, the negative surface charge of the oxyhydroxides, and their sorptive capacity for metals, increases with increasing pH. Conversely, the positive surface charge of the oxyhydroxides increases as the pH drops, making these phases more effective sorbents for anions under low pH conditions.

These effects are shown in Figure 4-3, which is a plot of percentage sorbed versus pH for metal adsorption by ferrihydrite, or HFO. The curves are called *sorption edges* for each metal. The diagram shows that the oxyanions are strongly adsorbed by HFO under acid conditions but are desorbed (become mobile) with increasing pH. Based on Figure 4-3, combined with adsorption data assembled by Dzombak and Morel (1990), the order of desorption from HFO with increasing pH is selenate, antimonate, molybdate, chromate, vanadate, arsenate, and phosphate. Selenate desorbs between pH 3 and 8, whereas arsenate is strongly held at lower pH values and desorbed between pH 9 and 11. Also based on Figure 4-3 and Dzombak and Morel (1990), with increasing pH, HFO preferentially adsorbs metals in the order $Hg^{2+} > Be^{2+} > Ba^{2+} > Cr^{3+} > Pb^{2+} > Cu^{2+} > Cd^{2+} \approx Zn^{2+} > Ni^{2+}$.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

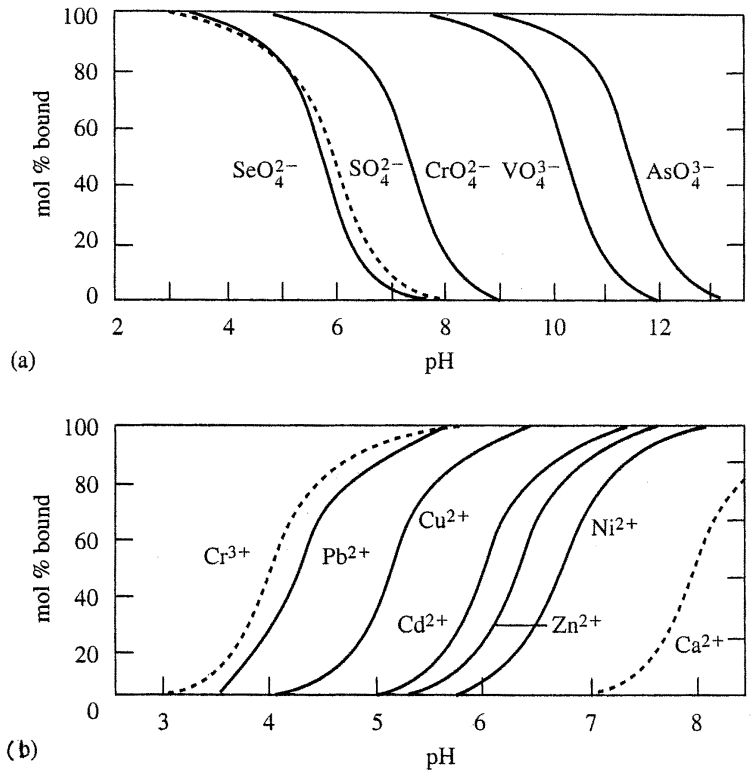

Figure 4-3. Adsorption of various metal cations and oxyanions, each at 5×10^{-7} M, by ferrihydrite ($\Sigma Fe[III] = 10^{-3}$ M) as a function of pH at an ionic strength of 0.1 mol/kg. There are 2×10^{-4} M of reactive sites on the oxyhydroxide. The dashed curves are calculated after Stumm (1992).

4.1.6.2.3. ***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 and phosphorus. On average, approximately 58% of organic matter is organic carbon. Soils encompass a range in organic matter, from <1% for a sandy soil to almost 100% for a peat soil, with most soils having organic matter contents <10% (Bohn et al., 1985). Also, organic matter content is usually higher in

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 to attract metal cations.

4.1.6.3. *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 over time. 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 onto organic matter and soil particles. These slow reactions are attributed to micropore diffusion, occlusion in solid phases by (co)precipitation and (co)flocculation, and cavity entrapment. Although the slow reactions play a key role in metal bioavailability, their rates, mechanisms, and controlling factors have not been comprehensively elucidated. Evidence of aging processes is provided by studies of metal extractability and lability (Young 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. Aging reactions are almost over after about 1 year and are 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.

4.1.6.3.1. *Steady-state calculations for metals in soils*

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

where d is soil depth in meters,
y is annual crop yield (t ha^{-1} y^{-1}),
TF is the ratio of the metal concentration in plant to that in soil,
R is the net drainage loss out of the soil depth considered (m^3 ha^{-1} y^{-1}),
K_d is the ratio of the weight of metal adsorbed to the weight of the sorbent, divided by the metal concentration in a volume of soil solution (L Kg^{-1}).

The time required to achieve 95% of steady state is about four half-lives. This is shown in Table 4-5 for select metals and metalloids. Selenium approaches steady state after only 1 year. As a consequence, Se soil concentrations after 100 years and at steady state are identical. In contrast, concentrations of Cu, Cd, Pb, and Cr(III) are still well below steady-state values after 100 years and, consequently, their concentrations in soil are very similar. The time necessary to approach steady state is a function of the loading rate and K_d.

Table 4-5. Time to achieve 95% of steady-state metal concentration in soil and total soil metal concentrations after 100 years and at steady state[a]

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

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

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

4.1.6.3.1.2. *Limitations*. It should be noted that the time needed to approach steady state for all the metals considered, except Se, is in the order of thousands of years, and it is difficult to

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

envision that soil conditions would not change in this time frame. However, the concept is useful because it provides a time frame within which to consider risk as a function of loading capacity of the soils and the potential for continued exposure even after cessation of anthropogenic inputs of metals to soils. Limitations on the application of K_d are discussed in Section 4.1.4.

4.1.6.3.2. ***Laboratory methods to simulate aging in soils***

4.1.6.3.2.1. ***Application.*** The aging effect requires laboratory studies on soils to apply a time-dependent weathering or aging treatment of spiked soils. Critical toxicity values generally are based on toxicological tests performed during the period of relatively fast metal adsorption that follows metal addition to soil. Such values would be lower than those derived from a similar study conducted with soils a year or more after addition of the metal. McLaughlin et al. (2000) proposed that toxicity thresholds be set using a sequential testing procedure. Tests would be conducted within 2 to 7 days following incorporation of the test substance to generate an estimate of acute hazard. Another set of soils would be tested 60 days after mixing, and a third would be subject to a leaching process and also tested after the 60-day period. It has been estimated in preliminary studies that toxicity is reduced up to 10-fold owing to aging of metals in soils. However, further studies are warranted and standardized processes should be agreed upon before metals aging can be properly accounted for in soil toxicity testing.

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

4.1.6.4. ***Dissolution and Transformation of Metals***

4.1.6.4.1. ***Application.*** The dissolution and transformation of a metal compound in soil is related to a series of chemical and physical properties characteristic of the compound itself and of the soil. Environmental parameters such as temperature and humidity have a strong influence on the rate of transformation. When assessing the transformation of a compound in soil, it should be remembered that aging reactions may take place at the same time as transformation and dissolution. When metal salts are added to soil, the form of the salt dictates the rate and amount of soluble metal that will form in the pore water. Insoluble forms of metals (e.g., vanadium pentoxide [V_2O_5]) will transform to soluble free ion (V) at a slower rate than will

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 relative rates of dissolution and aging should be considered simultaneously to accurately predict pore water concentrations.

4.1.6.4.1.1. ***Solution speciation (computer-based models).*** Computer-based models employ either equilibrium constants or Gibbs free energy values to determine metal speciation from solution chemistry conditions (concentration, pH, Eh, organic complexes, adsorption/desorption sites, and temperature). Both approaches are subject to mass balance and equilibrium conditions that should be defined. In recent years, as more accurate thermodynamic data have become available, the models have undergone extensive development and can provide useful predictive estimates of metal behavior. A good review of these models and their applications is provided by Lumsdon and Evans (1995). Examples of computer-based speciation models include MINTEQL, REDEQL2, ECOSAT, MINTEQA2, HYDRAQL, PHREEQC, and WATEQ4F.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.1.6.5. *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., Fe, Al, and Mn oxyhydroxides and organic matter) may have adsorptive surfaces that influence soil chemistry; (2) adsorption or precipitation of metals in soils or in roots limits uptake-translocation of most elements to shoots; and (3) the phytotoxicity of Zn, Cu, Ni, Mn, As, B, Al, and F, for example, limits residues of these elements 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 the soil-plant barrier

For strongly adsorbed metal cations, the pattern of plant response to metals contained in biosolids is strongly curvilinear (i.e., plant metal concentration approaches a plateau with increasing soil metal concentration), rather than being linear with increasing concentration. 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 equilibrated utilizing accepted methods.

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

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

4.1.6.5.1. ***Application/limitations.*** Strongly acidic soils increase plant uptake of Zn, Cd, Ni, Mn, and Co and increasl the potential for phytotoxicity from Cu, Zn, and Ni. In alkaline soils, the high pH increases uptake of Mo and Se. Lead and Cr are not absorbed by plants to any significant extent at any pH (Chaney and Ryan, 1993). However, each element 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-

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

solubility compounds with most of the metals of concern in soils, including Pb, Zn, Cd, Cu, and Ni (see above discussion on sediment chemistry). For essential elements (e.g., Zn, Cu, Ni), low-solubility species can result in deficiency syndromes. Upon oxidation of the soil, sulfide is quickly oxidized, and the metals are returned to more normal equilibrium reactions of aerobic soils.

4.1.7. Atmospheric Behavior/Chemistry

Most metals and metal compounds exist in the solid phase under ambient 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., Mn and Ni) may derive largely from crustal sources (U.S. EPA, 1996b). Richardson (2002) included volcanic eruptions and emissions, entrainment of soil and dust, entrainment of sea salt spray, and natural forest fires as significant metals emission sources.

For purposes of risk assessment, particle size is important. The aerodynamic size and associated composition of particles determine their behavior in the mammalian 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, 1996b). Metals emitted by combustion processes (e.g., the burning of fossil fuels or wastes) generally occur in small particles or the fine fraction, which is often characterized by particles less than 2.5 microns in diameter ($PM_{2.5}$). In contrast, the larger sized, course mode particles result from mechanical disruption, such as crushing, grinding, evaporation of sprays, or suspensions of dust from construction and agricultural operations. Accordingly, metals in course mode particles (i.e., those larger than approximately 1–3 microns) are primarily those of crustal origin, such as Si, Al, and Fe (U.S. EPA, 1996b). It is noted that 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 risk assessment (U.S. EPA, 1996b).

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, 1996b). 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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, 1996b).

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, 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 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.

Mercury is an exception among the commonly occurring metals; it exists primarily in the vapor phase under ambient conditions but can also occur in particle and aqueous phases. At least three species of mercury should be considered: elemental (Hg(0)) mercury, which is largely present as a gas; divalent (Hg(II)) inorganic mercury compounds, which are more water soluble; and particulate-phase mercury (Shroeder and Munthe, 1998; U.S. EPA, 1997b). The behavior of mercury in the atmosphere depends strongly on the oxidation state. Elemental mercury is capable of being transported long distances, even globally; divalent mercury deposits within a few hundred kilometers of sources; and particulate mercury is deposited at intermediate distances, depending on the particle size (Shroeder and Munthe, 1998). Elemental mercury that is deposited can be reemitted from the surface, as can divalent and particulate mercury after biological or chemical reduction to the elemental form.

In the gas phase, elemental mercury can be oxidized to divalent mercury by O_3, OH, H_2O_2 and molecular chlorine, although other halogen atoms might also be important (Shroeder and Munthe, 1998). In the aqueous phase, elemental mercury can be oxidized by OH, O_3, and

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

dissolved chlorine, and divalent mercury can be reduced by processes such as reaction with HO_2 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 mercury as a result of the requirements of the Clean Air Act. U.S. EPA (1997b) contains a comprehensive evaluation of mercury's atmospheric fate, but this is an area of ongoing research and controversy. EPA continues to be active in investigating mercury behavior in the atmosphere (e.g., Landis and Stevens, 2003; Jaffe et al., 2003; Bullock and Brehme, 2002; Bullock, 2000a, b; U.S. EPA, 2001a).

4.1.7.1. *Application/Limitations*

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., $PM_{2.5}$, PM_{10}, TSP), with subsequent analysis by x-ray fluorescence, atomic absorption, inductively coupled plasma, proton-induced x-ray emission, or neutron activation analysis gamma spectroscopy techniques. The one notable exception is a method for mercury (Method IO-5) that speciates vapor and particulate forms. To the extent that metals are sorbed to particulate phases, analysis of individual metal species can, at least theoretically, be accomplished by the same techniques used to analyze those species in other solid media.

4.1.8. Metals Speciation Techniques

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

4.1.8.1. *Particle-Bound Metal*

For particle-bound metal, tools include x-ray absorption spectroscopy (XAS), x-ray diffraction (XRD), particle-induced x-ray emission (PIXE and μPIXE), electron probe microanalysis-scanning electron microscope (EPMA-SEM), secondary ion mass spectrometry

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(SIMS), x-ray photoelectron spectroscopy (XPS), sequential extractions, and single-chemical extractions.

Over the past decade, numerous advances in materials science have led to the development of a wide range of analytical tools for determining metal concentrations, bonds, and valences of individual particles on a scale that can be considered useful for the speciation of environmentally important materials (soils, wastes, sediments, and dust). Although most of these tools are scientifically sound and offer important information on the mechanistic understanding of metal occurrence and behavior, only a few provide currently useful information on metal bioavailability for use at a "site" level (see Table 4-9 at the end of this section). However, other techniques still may be essential for conducting a detailed characterization of a selected material to describe the chemical or kinetic factors controlling the release, transport, and/or exposure of a metal.

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

4.1.8.2. *Single-Chemical Extractions*

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

4.1.8.3. *Plants*

When considering the bioavailability of a metal to plants from soil and sediments, it is generally assumed that both the kinetic rate of supply and the speciation of the metal to either the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

- *In situ* measurements using ion selective electrodes (Wehrli et al., 1994; Gundersen et al., 1992; Archer et al., 1989).

- *In situ* collection techniques using diffusive equilibrium thin films and diffusive gradient thin films followed by laboratory analyses (Zhang et al., 1995; Davison et al., 1994, 1991; Davidson and Zhang, 1994).

- Equilibrium models (WHAM/FREEQC/MINTEQA2).

4.1.9. Organo-Metals/Metalloids Transformation Processes

Metals/metalloids can exist in the environment in several valence forms and as organometallic compounds. *Organometallic compounds* (referred to in this section collectively as "*organometallics*") are compounds that have a metal/metalloid-carbon bond. The bonds in organometallic compounds are generally covalent and between soft 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, water, and atmospheric phases may be physically, chemically, or biologically mediated. Examples of some commonly occurring environmentally stable organometallic compounds are shown in Table 4-6.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-6. Some stable organometallic compounds

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

Environmental methyl-metal concentrations reflect the net methylation rather than simple rates of methyl-metal synthesis. Metal methylation and demethylation rates in ecosystems are influenced by the speciation and biochemical availability of the metal. Metals involved in abiotic or biotic methylation/demethylation processes are presented in Table 4-7. With the exception of arsenic and selenium, the metals listed in the table form stable complexes with either methyl or ethyl groups. In addition to methyl/ethyl compounds, stable organometallic compounds such as lipids and arsenic and amino acids and selenium are incorporated biochemically.

Table 4-7. Metals/metalloids involved in methylation processes

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

Source: Bodek et al. (1988).

Organometallic environmental transformations may affect both the mobility and the toxicity of these metals. *The rates of transformation and the organometallic products are dependent on environmental conditions and the population of microorganisms available.* For example, methylation/demethylation rates are dependent on the speciation of the metal, the microbial community, the environmental variables (e.g., pH, temperature, reduction oxidation potential, organic matter, dissolved oxygen, nutrient availability, salinity, complexing agents) and the distribution of the metal between compartments (sediment, water, gaseous). The inter-

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

relatedness of these processes has made research into unraveling the factors controlling net methylation difficult and, to date, incomplete. However, some general trends can be predicted with some certainty, and these are discussed in this section.

4.1.9.1. *Abiotic Transformations*

Organometallic compounds that are composed of metals with electronegativities >1.7 are the most stable under environmental conditions. Carbon-metal bonds with more polar (metal electronegatives <1.7) bonds will undergo hydrolysis (reaction with water). *Abiotic chemical methylation* can occur by three mechanisms: transmethylation reactions between mercury and tin/lead alkyls, humic/fulvic substances, and photochemical reactions.

4.1.9.2. *Biotic Methylation Transformations*

Biotic methylation occurs when organisms, primarily microorganisms, transfer alkyl groups to bioavailable metals. In general, it is thought that anaerobic sulfate-reducing bacteria are the principal methylators in freshwater and estuarine environments. However, methylation rates are not always correlated with sulfate-reducing bacteria. Not all sulfate-reducing bacteria are capable of methylating, and efficiency of methylation is dependent on the activity and structure of the bacterial community. Other bacteria may be involved in methylation. Biotic methylation occurs predominantly in the sediment column; however, because the water column by volume is much larger, water column methylation is important.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

to release of methylated metals from the soil and subsequent depletion of organometallic compounds in the soil. Therefore, pH effects on net methylation in a system are not fully understood. In freshwater ecosystems, where sulfate concentrations are typically low, increase in sulfate concentration increases methylation rates. However, in reducing environments, increasing sulfide concentration decreases methylation rates.

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

4.1.9.3. *Organometallic Transformation*

Organometallic methylation and demethylation rates are influenced by both speciation and bioavailability of the metal, the microbial community, and a large number of environmental factors, many of which are interrelated. Sulfide and organic matter are important environmental variables that significantly affect methylation; however, their effect on methylation/demethylation is as yet poorly understood. Which variables dominate differs among locations and between seasons, although it is clear that methylation is predominantly a biologically mediated process. Methylation/demethylation rates are strongly influenced by the metal/metalloid speciation and bioavailability. General trends in methlyation/demethylation rates are outlined in Table 4-8.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-8. General trends of environmental factors affecting rates of methylation/demethylation

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

↑ indicates an increase in rate.

↓ indicates a decrease in rate.

? indicates conflicting data or insufficient data to indicate a likely trend.

4.1.9.4. *Atmospheric Transformations*

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.1.9.5. *Aquatic Transformations*

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

4.1.9.5.2. ***Biotic Methylation/Demethylation Transformations.*** Microbial methylation processes play the major role in methylation of Hg, Sn, and As, with methylcobalamin the most likely environmental methyl donor. Metal speciation is a prime factor regulating the methylation potential in a system. Until recently, Hg^{2+} was considered the main mercury species methylated by bacteria; however, current research indicates that uncharged Hg complexes are more likely the principal species methylated (Ullrich et al., 2001). Arsenate can be reductively methylated (via arsenite) under anoxic conditions to dimethylarsine. Selenium and selenite can be methylated via microorganisms; demethylation of organoselenium via other biotic processes is also known.

4.1.9.5.3. ***Environmental Factors affecting methylation.*** Seasonal variation of methylated mercury is thought to be related to temperature, redox potential, and productivity. Seasonal variation for organic arsenic (dimethylarsenic) has also been reported, with organoarsenic species decreasing in late fall and winter.

4.1.9.6. *Terrestrial Transformations*

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

4.1.9.6.2. ***Biotic methylation/demethylation transformations.*** Plants have the capacity to transform metals and metalloids that are taken up from the soil. The most notable example is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

selenium. Soluble inorganic oxyanions of selenium are readily taken up by plants and converted to organoselenium compounds, such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide. Demethylation/dealkylation of organoselenium (e.g., trimethylselenonium), organomercury, organoarsenic, and organotin can occur in soil.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-9. Metal speciation techniques for solids and their associated pore waters

Tools	Species lability	Species particle size	Species valance state	Species bonding	Species composition	Species abundance	Element specificity	Isotopic character	Element sensitivity	Resolution	Availability	Cost
XRD	No	No	No	No	No[a]	No	No	No	3–4 vol%	Bulk	1	$
EMPA/SEM	Yes	Yes	Yes[b]	No	Yes	Yes[c]	B-U	No[d]	100 ppm	0.5–1 μ	2	$$
SIMS	No	Yes	No	No	Yes[e]	Yes[f]	Li-U	Yes	1 ppb	10 μ	4	$$$
XPS	No	No	Yes	Yes	Yes[e]	Yes[f]	H-U	No	wt.%	100 μ	2	$$
XAS	No	No	Yes	Yes	Yes[e]	Yes[f]	He-U	No	ppb	2 μ	5	$$$$
PIXIE	No	No	No	No	Yes	Yes[f]	B-U	No	10 ppm	4 μ	4	$$$$

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.2. HUMAN HEALTH EXPOSURE PATHWAY ANALYSIS

4.2.1. Introduction

This section and Section 4.3 discuss issues of importance when performing human health risk assessments for metals and metal compounds. The information provided will complement other general Agency guidance on the risk assessment process (e.g., Carcinogen Risk Assessment (U.S. EPA, 2003b), Exposure Assessment (U.S. EPA, 1992b), Developmental Toxicity (U.S. EPA, 1991b) and focuses on the unique and specific characteristics of metals and metal compounds that might be applied in metals risk assessments for human health. This section provides some of the scientific basis that underlies metal-specific characteristics of human health effects assessment, but it is not intended to be comprehensive. Appropriate and sufficient reference material provided in this framework document will guide readers to additional details on any of the topics addressed.

4.2.2. Human Exposure

Assessment of human exposures to 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. Although these components are common to exposures to human and nonhuman receptors, and to metal as well as nonmetal toxicants, some specific aspects of human metal exposure assessment are discussed below.

4.2.2.1. *Environmental Background Concentrations*

For assessments performed to assess impacts associated with particular human activities (e.g., hazardous waste sites, environmental releases), the term “ambient background” generally refers to all other sources of the metals of interest. The contribution of the background to human metal exposure may be significant. For example, metals are natural components of the environment and are repeatedly cycled throughout the biosphere (this component of the ambient background is referred to as “natural background”). Metals are also present as background from persistent anthropogenic activities. During the early 1970s, for instance, industrial sources

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

accounted for more than 90% of the airborne lead, the deposition of which supplied a large fraction of the lead in many ecosystems (Nriagu and Pacyna, 1988). Various strategies are available to estimate background metal concentrations in environmental media (soil, water, and sediment) (U.S. EPA, 1995a, b; 1989b), and a number of documents dealing with the background concentrations of metals in soils have been published by the U.S. EPA (2002b, c, d; 2001b, c).

Dietary pathways account for the major impact of background sources of metals. A number of sources provide information on dietary exposure background for 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). The prominence of diet in exposure assessment is discussed by Thomas et al. (1999). The United Kingdom also has extensive archives of metal content of beverages and infant foods (http://archive.food.gov.uk/maff/archive/food). Additional human dietary exposures may occur secondary to commercial processing of foods (e.g., use of preservatives, emulsifiers, taste enhancers, and packaging products that contain metals). Products such as liquid diets for weight loss, infant formula, and supplements for geriatric patients contain metals.

Exposure to metals in the diet can be high enough to approach or even exceed occupational or other well-known exposures to the metal (e.g., arsenic in drinking water). Thus, biomarkers (e.g., urinary arsenic, blood mercury) should take diet into account when estimating exposure. For example, in the 24 hours following ingestion of a seafood meal, the urinary arsenic concentration can often rise to 1 mg/L (WHO/IPCS, 1981). In contrast, persons living in Taiwan in an area with endemic arsenic contamination of the water supply of 50–300 µg/L had urinary arsenic concentrations of 140 µg/L (WHO/IPCS, 2001). Workers at a copper smelter where there was considerable arsenic exposure were found to have urinary arsenic concentrations in the range of 200–600 µg/L (WHO/IPCS, 2001). In a study of 380 American dentists, Brady et al. (1980) reported a mean concentration of 8.5 µg per litre, 7.4% of the participants having blood mercury levels greater than 15 µg/L (WHO/IPCS, 1991). In contrast, median cord blood mercury concentrations in a cohort with high fish consumption in the Faroe Islands was 24 µg/L (NRC, 2000). Mercury concentrations in the blood of people with long-term exposure to methyl mercury from fish were reported to be as high as several hundred µg/L (WHO/IPCS, 1990a).

Lifestyles expose people to metals in many different contexts and contribute to ambient background and total exposures. These exposures occur in the workplace, in nutritional

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

supplements, in pharmaceuticals taken by the oral and injection routes, in medical diagnostic procedures, in cosmetics, in recreational drugs (e.g., smoking), in folk medicines, and in paints and pigments. For example, cadmium from tobacco smoking can significantly affect a person's total exposure.

4.2.2.1.1. ***Application.*** Depending on the scope, purpose, and approach employed for the exposure assessment, background may be considered in different ways. For example, in the case of predicting exposure estimates from information on environmental releases of interest, background estimates may be included as well, and depending on the methodology, the risk estimates may be developed for the aggregate exposure as well as for the different sources of interest, including background. In this approach, differences in bioavailability among the various metal sources should be considered and incorporated into the calculation of total exposure. Alternatively, biomarkers may be used for exposure assessment, which already account for bioavailable fractions. Therefore, while it may not be feasible to partition out contributions specific to the pollutant source or exposure pathway of interest, biomarkers will provide an estimate of aggregate exposure.

4.2.2.1.2. ***Limitations.*** The approach taken for background may depend on the dose-response relationship for the health endpoint of interest. In the case of cancer assessments, where the Agency has derived a probabilistic relationship and the risk management decision framework is particular to the incremental risk of the pollutant source or human activity of interest, the basic background evaluation can simply focus on providing the foundation for that incremental context. Yet for many other health endpoints, the Agency's traditional approach for toxics involves the Reference Dose (RfD) or Reference Concentration (RfC) approach, which may be conceptually described as an uncertainty bound on a No-Observed-Adverse-Effect Level (NOAEL). The NOAEL by itself provides no information about the slope of the dose-response relationship or, therefore, the incremental change in risk expected for an incremental increase in exposure above the background level. Thus, in those cases, it will be more important for the exposure assessment to consider estimates of total, rather than incremental, exposures.

4.2.2.2. *Air Pathways of Exposure*

Air pathway inhalation is the major pathway for human intake of metals in which air serves as the primary medium of contact. Indirect pathways in which air serves as an antecedent

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

medium also include the following: deposition of metals to surface dusts and subsequent intake from ingestion or inhalation; deposition to surface water and sediment and intake from ingestion; and uptake of deposited metals into or onto aquatic and/or terrestrial biota, entrance into the human food chain, and intake from ingestion. Both systemic bioavailability and local actions on nasal mucosa, airways, and lung tissue should be taken into account when considering human health effects incurred via the air pathway.

4.2.2.2.1. ***Applications.*** Most airborne metals, with a few important exceptions (e.g., mercury and arsine) occur in particulate form, which necessitates certain considerations for inhalation exposure assessment. For example, particle size affecting 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, 1997c, as revised in 2004b). 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 (PM_{10}). Larger particles do not generally penetrate far into the respiratory tract and can be cleared to the ingestion route. They may play a larger role in irritant and other effects on 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 size of particles sampled is an important consideration.

For metals for which the Agency has developed RfCs and IURs, the exposure estimate should be for the form of metal used in the dose-response assessment that established the reference values (e.g., exposure concentrations, usually with focus on the respirable fraction) (U.S. EPA, 2004c). For more information on the consideration of particle size in the dose-response assessment for RfCs and IURs, refer to U.S. EPA, 1990. For metals for which the Agency has developed alternative dose-response metrics (e.g., blood lead concentration), respirability, deposition, and clearance as well as absorption into the circulatory system may need to be addressed as part of the exposure assessment.

4.2.2.2.2. ***Limitations.*** In developing inhalation exposure estimates, attention should be given 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, as it can with all exposure routes. Metal speciation affects a

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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; Oberdoerster, 1992). For example, in assessing the risk of inhaled chromium, 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 routes of intake. This may result in relatively high internal doses, even when intakes are similar to those from other routes. An example is the large contribution made by cigarette smoking to the body burden of cadmium (e.g., 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).

4.2.2.3. *Dust and Soil Pathways of Exposure*

Surface dusts and soil are particularly important media of human contact with metals. Both serve as long-lasting repositories for airborne metal particles, and soils also contain metals due to direct contamination from runoff or mixing with solid wastes. Humans are exposed to metals in surface dust and soil primarily through incidental ingestion or inhalation of suspended dust particles. Dermal contact with metals in soil represents another potential route of exposure, but the relatively low lipid solubility of most metals generally limits absorption through the skin (Paustenbach, 2000; Hostynek et al., 1998). Few studies have actually attempted to quantify the extent or kinetics of 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. Therefore, this exposure route is of lesser importance for most metal assessments than the ingestion and inhalation exposure routes.

Infants and children are particularly vulnerable to exposures to metals through the surface dust pathway because (1) their crawling and play activity put them in close proximity to surface dust, and (2) they often mouth their hands (e.g., finger sucking) and objects in their environment. This causes intakes of surface dust that are generally greater than those normally found in adults (e.g., Barnes, 1990). The amount of soil ingested by children can be expected to vary with numerous factors, including age, activity patterns, and accessibility to soil and dust. 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, 1994b).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Exposure assessment methods for direct soil ingestion is described in the Risk Assessment Guidance for Superfund (RAGS) (U.S. EPA, 1989b; 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) may be found in the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002e).

Few studies of soil ingestion in adults have been conducted; however, the estimates support the general assumption that average daily soil ingestion rates of adults who do not participate in activities in which intensive exposure to surface dust and soil occur (e.g., occupational gardening, construction work) are lower than those of children (Calabrese et al., 1990; Hawley, 1985). Because concentrations of the metal contaminants in soil can be expected to vary with depth, exposure assessments should consider soil metal concentrations at the depth appropriate to the metal(s) of concern and human behaviors and activities. The size of metal-bearing particles also varies with depth. For example, higher concentrations of lead and smaller particles are found near the soil surface (Duggan and Inskip, 1985; Duggan et al., 1985; Fergusson and Ryan, 1984). For review, see Chaney et al. (1988). Because bioavailability of lead and other metals increases with decreasing particle size (U.S. EPA, 2004a; Barltrop and Meek, 1979), both particle size and depth of contamination become very important considerations in metal exposure assessments.

4.2.2.4. *Dietary Pathway*

Food can be a major contributor to human metal exposures from contaminant point sources as well as containing trace amounts of naturally occur metals. Failure to accurately account for the dietary contribution can result in significant errors in exposure and risk estimates for metals (Choudhury et al., 2001). Human dietary exposures to metals may occur through various pathways. Livestock grazing in metal-contaminated areas can take up metals from soils or surface water. Metals also can migrate into surface water and sediments and can be taken up by aquatic organisms that are consumed by humans. Human food crops also can take up metals from soils and surface water or become contaminated with metals through deposition of airborne particles. Metals can enter food during harvesting or processing of produce and livestock, during food storage from metals in food containers, and during preparation of foods for meals.

4.2.2.4.1. *Application*. Estimation of intakes of metals in food requires information or estimates on the levels of the metal in food and the amount of food consumed. Although large-scale

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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), these surveys have several limitations for applications to risk assessment at a contaminated site. Analysis is often conducted with "market basket" samples of packaged processed foods. With few exceptions, such applications have not been empirically evaluated against biomarkers of exposure (Clayton et al., 2002, 1999; Choudhury et al., 2001). For some risk assessments, multimedia fate and transport models may be used to predict concentrations in locally grown or raised foods or wildlife consumed by the population of interest.

4.2.2.4.2. ***Limitations.*** Because some metals (e.g., cadmium and lead) could have long residence time in the body, reconstructing historic dietary exposures can be a challenge. Food consumption surveys generally are limited to short-term consumption (e.g., 1 to 3 days) and do not capture intra-individual variability that would affect long-term averages. Furthermore, food consumption patterns can be expected to change over time; thus, patterns discerned at any given time may not accurately represent historical exposures. An additional challenge is the integration of data from separate metal residue surveys and food consumption surveys (e.g., Tomerlin et al., 1997). This leads to considerable uncertainty in estimates of metal exposure through the dietary route.

Furthermore, estimates of dietary intakes of metals in food based on national or regional data cannot be expected to accurately reflect intakes of metals in locally harvested foods owing to differences in natural background levels of metals. This can be a particularly important limitation when the receptors of concern are subsistence fishermen or hunters. These surveys also may not accurately reflect the amount of metals that enter the food pathway during local food preparation or storage (e.g., in the home).

4.2.2.5. ***Water and Sediment Pathway***

Part of the human population obtains drinking water from untreated sources, such as wells. However, people also consume water specifically treated for human consumption. Treatment of ambient water for human consumption removes DOC and suspended organic sediments that can form complexes with metals (AWWA, 1999). Thus, the exposure context of metals in human drinking water will be very different from that of ambient water. That is, inorganic forms of metals in treated drinking water will consist of the more bioavailable, water-

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

soluble species. Treatment also removes bacteria that can participate in organification reactions of toxicological significance to humans (e.g., methylation of inorganic mercuric mercury).

4.2.2.5.1. ***Applications.*** Estimation of the intake of metals in drinking water requires information about or estimates of concentrations of metals in the water and the amount of water consumed. Data on the metal content of tapwater can be obtained from EPA's Office of Drinking Water (U.S. EPA, 2000d). 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, 1997h). People also can be exposed to metals dissolved in ambient surface water or in association with suspended sediments; the latter can serve as a long-term repository for waterborne metal particles. Such exposures occur during swimming or other recreational activities as a result of incidental water ingestion or during occupational activities in which the sediments are disturbed or resuspended in the water column. Metal bioavailability in ambient surface water can be expected to be much more diverse than in treated drinking water or in ground water because of the presence of organic carbon, inorganics, and suspended organic material that can serve as ligands or reactants for metals. Speciation and concentration will also vary with pH of the surface water. Therefore, estimation of intake of metals from surface water will require appropriate adjustment for relative bioavailability.

4.2.2.5.2. ***Limitations.*** Metals can enter treated drinking water at various stages of water treatment, distribution, or delivery. Generally, water metal concentrations are measured at the distribution point for municipal water delivery systems. Distribution systems within homes (pipes, storage containers, etc.) and, in the case of lead, glassware, can contribute metals to the water (Graziano et al., 1996). The contribution of metals from pipes (either from the distribution system to the home or within the home) is rarely assessed. This can be highly variable, both within the system and temporally; water that remains in pipes overnight frequently has a higher metal load than water used during the day. Furthermore, the concentration of organic material and other ligands in the water may vary across drinking water sources and can affect the bioavailability of the metal. There is also wide variability in the form of metals in ambient surface water. These factors can be incorporated into site-specific assessments, but local data should be collected on a case-by-case basis. Inhalation of inorganic metal contaminants in water can result from aerosolization, or in special cases, from volatilization (e.g., Hg^0). The aerosolization pathway can be a major source of intake of inorganics under certain conditions.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

As an example of aerosol exposure, sea spray can be a significant contributor to iodide intakes in populations that live near the seashore (Whitehead, 1984). A pathway more typical of human exposure to contaminated water is showering, in which areosolization can occur at the water tap. Although models have been developed to predict human inhalation exposures to volatile organics from showering (e.g., Moya et al., 1999; McKone, 1987) (see Guo, 2002, for review), comparable models do not exist for aerosolized metals (Wilkes, 1998), and the magnitude of exposure from showering is unknown.

4.2.3. Routes of Entry

The most frequently encountered routes of entry of metals into humans are ingestion and inhalation. The dermal route is of less concern for most metals but can be important for skin toxicity of some metals (e.g., nickel, chromium). Other routes can be important in specific circumstances, for example, explosions of metal-bearing materials can result in intra- or trans-dermal exposures (Robinson et al., 1983). It is also important to remember that metals can produce toxicity at the point of entry. While metal absorption from skin may be minimal, dermal irritation and sensitization can occur without absorption. Similarly, human health effects such as lung disease and lung cancer can occur from inhalation exposures that do not result in substantial systemic uptake. Routes of entry do not necessarily correspond to the expected exposure pathway. For example, uptake of airborne metals associated with larger particles can actually be attributed to ingestion of surface dust rather than absorption from the respiratory tract. The significance of this process relative to other pathways will depend on the exposure scenario generally being less significant than diet or soil ingestion pathways (see sections 4.2.1 and 4.2.2.2). Thus, uptake in the lung can be the source of exposure by two routes.

Although dermal contact with metals occurs through soil, air, and water pathways, the relatively low lipid solubility of most metals limits absorption through the skin (Paustenbach, 2000; Hostynek et al., 1998). An exception is Hg^0, which is dermally bioavailable (Hursh et al., 1989). In general, empirical information on dermal absorption of metals should be consulted when available (Stauber et al., 1994; Hostynek et al., 1993; Wester et al., 1992; Hursh et al., 1989; Ilyin et al., 1975).

4.2.4. Integrated Exposure Approaches

Approaches to integrating exposure across pathways and physiological routes of uptake include modeling, relative bioavailability estimates, and biomarker assessment.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.2.4.1. *Modeling*

Few specific exposure models have been developed for metals with the exception of lead. The Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in children (White et al., 1998; U.S. EPA, 1996c, 1994b) was specifically developed for translating exposure measurements into risk estimates at sites contaminated with lead. The IEUBK model and background documentation are available on line at http://www.epa.gov/superfund/programs/lead/ieubk.htm. The IEUBK model assumes that 10 µg/dL is a no effect level, while current science indicates there may be no safe level of lead exposure. The model is not readily generalized to other metals because blood lead levels are used as the dose metric, and dose-response assessment for most other metals use estimates of oral or inhalation intake rates.

A stochastic human exposure model for lead that is linked to a lead pharmacokinetics model (O'Flaherty et al., 1995) has also been developed (Beck et al., 2001). Less complex models linking adult exposures and blood lead concentrations are available as well (Carlisle, 2000; Stern, 1996, 1994; U.S. EPA, 1996c; Bowers et al., 1994; Carlisle and Wade, 1992). These models have not been reviewed by the Agency authors. An exposure model for arsenic has also been reported (Cohen et al., 1998).

Other general exposure models used in risk assessment can be potentially applied to metals, including population-based models. The EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model is a probabilistic, physiologically based model that simulates aggregate human exposures and doses (i.e., via inhalation, dietary, dermal, and nondietary routes) for population cohorts and multimedia, multipathway chemicals of interest (Zartarian et al., 2000). EPA recently has applied the SHEDS model to estimate arsenic exposure of children from chromated copper arsenate (CCA)-treated wood (Dang et al., 2003). EPA has also developed a Dietary Exposure Potential Model (DEPM) that links national food consumption and chemical residue data to allow estimates of average dietary intakes of metals and other food contaminants (Tomerlin et al., 1997). EPA's Total Risk Assessment Methodology (TRIM) is also being developed for multipathway risk assessment for air pollutants, including metals (See http://www.epa.gov/ttn/fera/trim_gen.html). A generic exposure model, RESRAD, developed by the U.S. Department of Energy for risk assessment of radionuclides (U.S. DOE, 2001; LePoire et al., 2000), includes an extensive human exposure module applicable to other metal contaminants.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.2.4.2. *Relative Bioavailabililty*

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

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

The EPA Office of Solid Waste and Emergency Response (OSWER) has used bioavailability information in making quantitative adjustments. In 1989, OSWER published a risk assessment guidance for use in human health risk assessments at Superfund sites and has updated this guidance periodically (U.S. EPA, 1989b). This guidance recognizes that the toxicity of an ingested chemical depends on the degree to which it is absorbed from the gastrointestinal (GI) tract into the body. Thus, adjustments to bioavailability assumptions were developed to account for differences in absorption efficiencies between the medium of exposure and the medium from which the toxicity value was derived. Further, because RfDs and CSFs are generally expressed in terms of administered dose rather than absorbed dose, it also discusses the need to adjust for differences in the expression of dose between the exposure and toxicity value (e.g., absorbed vs. administered dose). The Agency guidance recommends that the relative bioavailability adjustment (RBA) of a chemical should be assumed to be equal in food, water, and soil in the absence of data to the contrary.

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

4.2.4.2.2. ***Current Practice.*** The Agency currently addresses bioavailability through the use of default values and, in some cases, through the development of site-specific and medium-specific values. To date, the most common treatment of bioavailability for human health assessments is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

to assume that the bioavailability of the metal exposure from the site is the same as the bioavailability of the source used to derive the toxicity value (RfD or CSF). The RfD and CSF are typically developed from laboratory toxicity tests using highly bioavailable forms and are usually based on administered rather than absorbed doses. This is true for all chemicals, but it is of special importance for ingested metals because metals can exist in a variety of chemical and physical forms, and not all forms of a given metal are equally well absorbed. For example, a metal in contaminated soil may be absorbed to a lesser extent than when ingested in drinking water or food.

It is important to recognize that a default RBA value of 1 (100%) is not necessarily conservative (i.e., more protective of human health). The bioavailability of the metal in the exposure medium of concern at the site may actually be greater than in the exposure medium used in the critical toxicity study that formed the basis of the RfD or CSF. If this is the case, assuming RBA of 1 for the medium of concern would result in an underestimate of risk at the site. The Agency recognizes that some cases may exist where sufficient data are available to support development of medium-specific default absorption factors for a particular chemical. The purpose of these medium-specific and chemical-specific default values is to increase the accuracy of exposure and risk calculations even when site-specific studies are not available.

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

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

The Agency has also derived RfDs that are specific for an exposure medium, based on consideration of bioavailability or other factors that might suggest unique dose-response relationships in that medium. For example, separate RfDs for cadmium in food and drinking

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

water have been derived through the rationale that the bioavailability of cadmium in water is greater than that of cadmium in food by a factor of 2 (i.e., 5% vs. 2.5%, respectively [U.S. EPA, 2003f]). Similarly, the Agency recommends that a modifying factor of 3 be applied to the chronic oral RfD for manganese when the RfD is used to assess risks from drinking water or soil to account, in part, for potential differences in bioavailability of manganese in water and soil compared to that in food (U.S. EPA, 2003g). Therefore, use of default values should not substitute for site-specific assessments of bioavailability, where such assessments are deemed feasible and valuable for improving the characterization of risk at the site.

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

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

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

The principal advantage of whole-animal oral chemical absorption studies is that they measure bioavailability in its most clinically relevant form, that is, from the GI tract and into the systemic circulation. This integrates all of the relevant biological components related to systemic absorption, including pre-systemic elimination, if present. By using the animals as surrogates for humans, these studies avoid the experimental and ethical problems associated with the use of human subjects. Currently, certain in vivo bioavailability studies conducted with an

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

appropriate species are considered the gold standard for developing bioavailability information suitable for use in quantitative human health risk assessments, and they are often used to validate other bioavailability tools. For example, the young swine model for lead bioavailability has been used to validate in vitro extraction tests.

4.2.4.2.3.1. ***Animal Model Applications*.** Animal models have served as the basis for making site-specific bioavailability adjustments at several Superfund sites. Scientists from EPA Region 8 sponsored the development of whole-body *in vivo* bioavailability studies in juvenile swine as a model of young children who were exposed to lead in soil contaminated with various forms of mine wastes (Lavelle et al., 1991; Weis et al., 1992, 1993a). The results of these efforts were subjected to outside peer review and found to be valid and acceptable for use in adjusting the RBA for lead in human health risk assessments. As a result, the juvenile swine model is presently being used as the preferred animal model for lead (U.S. EPA, 2004a). Site-specific bioavailability adjustments based on results from the juvenile swine model have been accomplished at several sites across the country, including the Murray Smelter in Colorado; Palmerton, PA; Jasper County, MO; Smuggler Mountain, CO; and the Kennecott site in Salt Lake City, UT.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.2.4.2.3.2. ***Animal Model Limitations.*** Currently, bioavailability studies conducted with an appropriate animal species are considered the most reliable for making quantitative bioavailability adjustments in human health risk assessments. They are also used as a means to validate other tools, such as physiologically based extraction tests. However, animal models are generally complex, time consuming-, and much more expensive than other tools. As a result, use of animal models is usually limited to large sites where it is difficult to adequately characterize the variability in bioavailability across the site. An investigator must ensure that the study design and animal model selected are appropriate for the metal being tested. The best measure of bioavailability (blood vs. tissue vs. feces vs. urine) is dependent on the pharmacokinetics of a particular compound. As discussed above, each measure has its own inherent limitations. Further discussion of the limitations of animal models are discussed elsewhere (NAS/NRC, 2002; NFESC, 2000a, b).

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

4.2.4.2.4. ***In vitro Methods.*** Recently, significant effort has been expended on developing *in vitro* methods for assessing the RBA of metals, due to their ease of use and potential cost savings when compared against more traditional *in vivo* methods using laboratory animals. Several researchers have investigated *in vitro* models that attempt to simulate the conditions in the GI tract (Drexler et al., 2004; Medlin, 1997; Rodriquez et al., 1999; Ruby et al., 1993, 1996, 1999) and which are often referred to physiologically based extraction tests. These methods are based on the concept that the rate and/or extent of metals solubilization in GI fluid is likely to be an important determinant of metals bioavailability *in vivo*. These assays provide a measure of bioaccessibility or the amount solubilized in the GI fluid and available for potential absorption (Ruby et al., 1993).

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

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

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

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

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

One of the key limitations of this approach is adeptly defined in NAS/NRC (2002):

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

OSWER is currently developing a bioavailability document on metals to advise risk assessors and managers on whether to collect site-specific information on the bioavailability of metals in soil and how to evaluate bioavailability data for use in human health risk assessments. The document will outline a decision framework that explains how to use bioavailability data consistently as part of a human health risk assessment. The decision framework will consist of a two-tiered approach. The first tier presents general guidelines for determining whether bioavailability is worth considering at a particular site. The second tier involves an ordered process for the actual collection and analysis of bioavailability data.

4.2.4.3. *Biomarkers*

Integration of exposures across media, route, and time of exposure can be reflected in biomarkers of exposure. The World Health Organization (WHO/IPCS, 1993) defines a biomarker of exposure as "an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism." Ideally, there should also be a well-established relationship between biomarker of exposure and outcome, in that the biomarker not only provides information about exposure levels but also can be predictive of an effect. For example, urinary

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

cadmium is directly correlated to the concentration of cadmium in the renal cortex, which is one site for toxicant action of this metal.

4.2.4.3.1. *Application*. In the case of metals, urinary cadmium and blood lead are examples of exogenous substances used as biomarkers of exposure. The measurement of metals in biological fluids has been used as the primary means of quantifying biomarkers of exposure for metals by occupational health organizations such as the American Congress of Governmental Industrial Hygienists. An interaction between a metal and a target molecule, such as the adduction of chromium(VI) with DNA and protein, is used to a more limited extent. Some biomarkers of exposure such as the DNA adducts of chromium(VI) fall into the area of transition in the continuum from exposure to effect.

For many of the metals of interest, biomarkers of exposure and effect are used as basic tools for population or molecular epidemiology studies of effects of exposure to humans of various metals. The Centers for Disease Control and Prevention (CDC) conducts an extensive biomonitoring program of human blood and urine that includes lead, mercury, cobalt, uranium, antimony, barium, beryllium, cesium, molybdenum, platinum, thallium, and tungsten (CDC, 2003). The data are summarized in age, gender, and ethnicity categories.

4.2.4.3.2. *Limitations*. A biomarker of exposure is a measure of cumulative exposure to a metal and also of metal actually existent in the body, as occurs with chronic exposure for metals. However, such an approach may not be appropriate for metals that are not extensively accumulated 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.

There are environmental (water, air, soil, dust), occupational, medicinal, and dietary sources of metal exposure. For this reason, use of biomarkers increases the need for comprehensive, multi-pathway assessments of exposure. Reference or background levels of biomarkers of exposure are essential for any assessment. Failure to consider background dietary sources of metals may result in a misinterpretation of the exposure. For example, arsenobetaine is a nontoxic organic form of arsenic found naturally in shrimp and other seafood. The analysis of total unspeciated urinary arsenic of individuals who consume seafood, without recognition of their diet history, will lead to an overestimation of exposure to potentially toxic (inorganic) arsenic species—some assessments of arsenic exposure have assumed that 10% of total

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

elemental arsenic in seafood and 100% of arsenic in all other foods is in a toxic, inorganic form (NAS/NRC, 1999).

The correct frequency and timing of sampling of biological fluids and tissues, as well as the correct interpretation of the results, depend on knowing the elimination half-life of the metal. The half-life of lead in plasma, blood, soft tissues, and bone ranges from hours to months to years (Sakai, 2000). A detection of lead in plasma above background levels would be indicative of an acute exposure, whereas a detection in bone would be indicative of chronic exposure. Thus, sampling plasma every other day or week, or analyzing bone, would not be the best way to determine whether an acute exposure to lead occurred.

The validity of a biomarker is supported by three kinds of relevance: analytical, toxicokinetic, and biological (Schulte and Talaska, 1995; Grandjean et al., 1994; WHO/IPCS, 1993). Key analytical issues include specificity, sensitivity, standardization of methodologies (to reduce intra- and interlaboratory variability), speciation, quality assurance, and the availability of reference samples. Analytical methods for the detection of metals include ICP-MS, hydride generation atomic absorption, and fluorescence spectrometry. When coupled with high-performance liquid chromatography, these methods are enhanced because of the ability to detect speciated parent metal and metabolites. Although these methods can be very reliable for the analysis of metals in biological fluids, using them for tissue analysis is more difficult. Digestion and extraction make it difficult to fully speciate the metal and produce interfering matrix factors. Reference standards for tissues are seldom available. X-ray fluorescence spectrometry, used to detect lead in bone (Ambrose et al., 2000), and neutron activation analysis, used for manganese in liver (Arnold et al., 1999), are highly powerful noninvasive in vivo techniques; however, the sensitivity is extremely limited. A disadvantage of any in vivo method is that the metal species in the environmental exposure cannot be estimated correctly.

4.2.5. Toxicokinetics and Toxicodynamics

Several specific properties of metals that affect their absorption, distribution, metabolism, and elimination can be identified. These properties of metals can influence their physiological handling as compared to organics (Table 4-10) and should be taken into account in pharmacokinetic analyses related to human health risk assessment. Properties that affect toxicodynamics should also be taken into account in these analyses.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-10. Metal (versus organic) compound properties affecting absorption, distribution, metabolism, and elimination

Organic compounds	Metals
Metabolism is generally extensive and often species-specific.	Metabolism is usually limited to oxidation state transitions and alkylation/dealkylation reactions.
Persistence in body fat is common because of lipid solubility (not capacity-limited).	Often sequestered, bound to specific plasma or tissue proteins (intrinsically capacity-limited) or bone.
Predominantly eliminated by excretion in urine and exhaled air after biotransformation from lipophilic forms to hydrophilic forms.	Predominantly eliminated in urine and bile. Metal compounds are hydrophilic.
Tissue uptake is most commonly a blood flow-limited process, with linear portioning into tissues.	Metals and their complexes are often ionized, with tissue uptake (membrane transport) having greater potential to be diffusion-limited or to use specialized transport processes.
Interactions with other structurally similar compounds may occur, especially during metabolism.	Interactions among metals and between metals and organics are numerous and occur commonly during the processes of absorption, excretion, and sequestration.

The evaluation of toxicodynamics addresses the sequence of biochemical events at the cellular and molecular levels that begin when toxicologically active form of the metal interacts with the target (e.g., from molecule to a protein, enzyme, or other cellular molecule, that leads to a toxic physiological response. Toxicodynamics involves the biological processes that underlie the severity of an effect as well as its reversibility, recovery, and adaptive response. These evaluations are applied for single metals as well as for metal mixtures, recognizing that one metal can induce multiple effects (from critical to secondary and more, as the exposure levels increase) and common effects can be exerted across many metals. To assure that effects are appropriately combined, it is important to reflect the underlying mechanism or mode of action; the potential influence of toxicokinetic processes should be considered (e.g., changes in gastrointestinal absorption and liver and kidney retention can change liver and red blood cell functions).

Two properties of metals, their hydrophilic nature and their characteristic protein binding, are discussed in more detail below, followed by a discussion of available physiologically based pharmacokinetic (PBPK) models.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.2.5.1. *Hydrophilic Properties of Metals*

Solubility in aqueous media is one of the major factors influencing absorption of metals and metal compounds. The water solubility of a metal compound depends on its chemical species, on the pH of its medium (H+ ions), and on the presence of other chemical species in the medium (see Section 4.1). Nitrates, acetates, and all chlorides of most metals except silver, mercury, and lead are soluble. Sulfates of most metals are also soluble, except for barium and lead. On the other hand, most hydroxides, carbonates, oxalates, phosphates, and sulfides are poorly soluble. Another factor influencing absorption of poorly soluble compounds is particle size: fine particles are usually more soluble. Metallic lead in body tissues (as may occur following gunshot wounds) is probably absorbed after being oxidized to soluble salt. Metallic mercury is corrosive when embedded in body tissues, but metallic mercury swallowed into the gastrointestinal tract is not soluble (Goyer and Clarkson, 2001).

The relative hydrophilic nature of metals versus organic compounds influences absorption at different sites. Absorption of metals in the gastrointestinal tract is hindered by the lipid nature of intestinal cell membranes but is favored by solubility in the hydrophilic contents of the gastrointestinal tract (preabsorption). In the lungs, the absorption of aerosols of particulate forms of metals and metal compounds and of lipophilic organic compounds may not be as dependent on the lipophilic or hydrophilic nature of the substance, depending more on particle size and on whether the substance is presented as a vapor or a gas (e.g., elemental mercury). Human skin is not very permeable and provides a good barrier against absorption of metals and metal compounds as well as highly lipophilic organic compounds. Elemental mercury and dimethyl mercury (Siegler et al., 1999) are notable exceptions. When dermal absorption does occur, the mechanism may differ between organic substances and metals. Polar substances, like metal compounds, appear to diffuse through the outer surface of protein filaments of the stratum corneum, which is hydrated, whereas lipophilic nonpolar organic molecules diffuse through the lipid matrix between the protein filaments (Rozman and Klaassen, 2001).

Hydrophilic metal ions do not readily diffuse into richly lipophilic tissues, such as the brain, liver, and neutral fat stores, where they would be difficult excrete. Although biotransformation of metals occurs, the products typically maintain a hydrophilic profile. Entrance of metals or inorganic metal compounds into lipid-rich tissues like the brain depends on hydrophilic pathways. Retention in tissues of metals or metal compounds is generally related to formation of inorganic complexes or metal protein complexes (e.g., lead in bone and cadmium in tissues bound to the low-molecular-weight protein metallothionein).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Although the low lipid solubility of metal ions could limit their accessibility to tissues and cells, recent rapid progress in identifying metal transporters (Foulkes, 2000) suggests that generalizations are not appropriate, and each metal should be assessed in terms of its ability to access transporters and of the presence of transporters in potential target organs. Furthermore, complex lipids can offer high-affinity binding sites for metal ions that promote their distribution to lipid compartments, and some metals, such as thallium, have a demonstrated affinity for adipose compartments.

Generally, the primary factor that influences the uptake and distribution of organic substances within the body is the substances' lipophilicity. Passage through cellular membranes and partitioning to organs occurs primarily through passive diffusion through the lipid portions of cellular membranes. Metabolism (or lack thereof) can, of course, influence the distribution and excretion of organic chemicals primarily because of the accompanying changes in chemical structure and, therewith, lipophilicity. The uptake, distribution, metabolism and excretion of an organic chemical can often be predicted by consideration of the substance's chemical structure and lipophilicity (i.e., octanol/water partition coefficient).

In contrast to organic substances, the uptake and distribution of metals in inorganic forms is generally influenced by atomic size and charge, and the availability of active cellular processes that naturally exist for the uptake and distribution of nutritional metals (e.g., calcium, sodium, potassium, magnesium) that can also transport other metals into or across cell membranes. The assumption of linear partitioning in tissues commonly applied to organics, and which is largely lipophilicity-based, is therefore not appropriate for the capacity limited processes that generally control the uptake and disposition of metals. Rather, the uptake, distribution, metabolism, sequestration, and mechanisms of action of metals is generally considered in the context of their kinetic behavior.

Metals can have residence times in the body as long as months or years, particularly when they are bone-seeking elements or are associated with tissue storage proteins. Metals, such as lead, strontium, and uranium, may be incorporated into bone, stored there, and many years later may be released from the bone tissue into the systemic circulation to sites of toxic action, by mechanisms closely linked to bone metabolism. These mechanisms include incorporation and loss with bone formation and resorption and, depending on the ionic radius and charge of the metal, can include migration within the bone complex as well as out of the bone (O'Flaherty, 1998). While long-term deposition of a metal (e.g., lead) in a tissue (e.g., bone) may not necessarily result in toxicity to that tissue, subsequent release of that metal from that tissue enables transportation of the metal to its site of toxic action elsewhere in the body. It is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

important for the risk assessor to consider the potential toxicological consequences of storage or deposition of metals in body compartments as part of the overall human health assessment.

Modeling the kinetics of metals with extended tissue residence times presents challenges in that anatomical and physiologic functions, along with changes in exposure, need to be characterized as a function of age and clinical status. For example, bone turnover is rapid in children and relatively quiescent in adults, but is increased in adults during conditions such as menopause, pregnancy, and lactation, to name a few. Ninety to ninety five percent of the adult human body burden of lead is contained in the bone. However, lead is not permanently fixed in bone tissue, but returns to the blood as bone is resorbed and by return from the bone surface (O'Flaherty, 1998). Gulson et al (1995) observed that between 45 and 75 percent of blood lead in a group of adult women had originated from the bone. Physiologically based kinetic models have been developed or are in the process of development for arsenic, lead, chromium, and mercury (O'Flaherty, 1998).

4.2.5.2. *Metal-Binding Proteins*

Metals react with many different proteins in the body that may modify kinetics. Many metals bind with albumin for purposes of transport in the circulatory system and across cell membranes and within cells. However, research is identifying a growing number of proteins that play specific roles in transport, cellular uptake, and intracellular storage of metals (Goyer and Clarkson, 2001), including the following:

- **Transferrin.** Transferrin is a glycoprotein that binds most of the ferric ion in plasma and has a role in transporting iron across cell membranes. This protein also transports aluminum and manganese.

- **Ceruloplasmin.** Ceruloplasmin is a copper-containing glycoprotein oxidase in plasma that converts ferrous to ferric iron, which then binds to transferrin.

- **Membrane carrier proteins.** A number of recently discovered carrier proteins transport metals across cell membranes. Many of these carrier proteins are multispecific (e.g., divalent metal transporter 1 and 2, metal transporter protein 1), Some metals are transported as complexes with endogenous ligands; no transport systems are intended for the ligand itself, accepting substrates that vary considerably but are recognized by the attached metal ion (Dawson and Ballatori, 1995).

- **Metallothioneins.** The metallothioneins are a group of low-molecular weight (MW) proteins (MW about 6,000 daltons), rich in sulfhydryl groups that serve as ligands for

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

several essential and nonessential metals. In vitro studies have found that the highest affinity is for silver, then in descending order mercury, copper, bismuth, cadmium, lead, and zinc (Kagi and Kogima, 1987). However, studies of in vivo metallothioneins from various sources included zinc, copper, and cadmium. Metallothioneins have multiple binding sites that have different affinities for metals. Also, the types of metals bound to metallothioneins differ depending on the species, the organ, and previous exposures to metals, but most of them contain at least two different types of metals. For example, metallothioneins isolated from adult or fetal human livers contain mainly zinc and copper, and those from human kidneys contain cadmium, copper, and zinc (Cherian and Goyer, 1995). In most cases, the metallothioneins are inducible and perform a number of functions, including serving as a storage protein for zinc and copper in the liver, kidney, brain, and possibly skin and having an important protective role in cadmium toxicity (Goyer and Clarkson, 2001). Although metallothioneins have an affinity for lead in vitro, in vivo binding to lead has not been demonstrated. Also, mercury may induce synthesis of metallothionein in vivo, but binding is only temporary regardless of the demonstrated in vitro affinity.

- **Ferritin.** Ferritin is primarily a storage protein for iron in reticuloendothelial cells of the liver, spleen, and bone. It plays an important role in turnover of iron. It has also been suggested that ferritin may serve as a general metal agonist because it binds a number of metals, including cadmium, zinc, beryllium, and aluminum.

- **Lead-binding protein(s).** Lead binds with a number of lead-binding proteins, but their identity or function is not as well defined as that of other metal-specific proteins. The most studied lead-binding protein is the denatured lead-protein complex identified as the intracellular inclusion body occurring in cells, particularly in the liver and kidney in persons with high-level lead exposure. It has been suggested that lead-binding proteins may have a protective effect for lead (Goyer and Clarkson, 2001).

4.2.6. Pharmacokinetic/Pharmacodynamic Modeling of Metals

Physiologically based pharmacokinetic/physiologically based pharmacodynamic (PBPK/PBPD) modeling of metals entails the mathematical description and modeling of a substance's behavior in the body (e.g., absorption, distribution, metabolism, excretion, and toxic effects). PBPK and PBPD models are valuable risk assessment tools for interspecies, high-dose/low-dose, route-to-route, and exposure scenario extrapolation (Krishnan and Andersen, 1994). PBPK models consist 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. PBPK models that include a fetal compartment are

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

particularly valuable for human metal risk assessment. In utero exposure can be important for establishing the body burden of certain metals before birth that result from transplacental transfer.

PBPK models have historically been developed and used for risk assessment of volatile organic compounds (VOCs) (e.g., methylene chloride) (Andersen et al., 1987) but have also been applied to many metals (White et al., 1998; Clarke, 1995). Metals differ in their kinetic behavior from VOCs in a number of ways, as discussed by O'Flaherty (1998). Guidelines exist for model evaluation, and these should be used as a framework to determine whether a particular model is appropriate for use in risk assessment (Clark et al., 2003; Andersen et al., 1995).

4.2.6.1. *Application*

Combined use of PBPK and PBPD models provides understanding of the complex relationships between exposure and target organ effects. PBPK models are often capable of predicting aggregate exposures for comparison to exposure models.

For metals that have long retention times in tissues, the maternal tissues can serve as a reservoir for exposures during fetal development. This can be a particularly important exposure pathway for metals that accumulate in the inorganic matrix of bone (e.g., lead, strontium, uranium) because mobilization of bone minerals to develop the fetal skeleton can result in a transfer of maternal bone stores of metals to the fetus (e.g., Gulson et al., 1999a, b; Tolstykh et al., 1998). Transplacental exposures cannot be directly measured from environmental measurements but require the use of PBPK models. A few models of transplacental transfer of lead in humans have been developed; models for other metals are not available for use in risk assessment. The lead models reported to date are limited in that they rely on assumptions of a steady state between maternal and fetal blood lead concentrations (U.S. EPA, 1996c, 1994b; Leggett, 1993; O'Flaherty, 1993). This assumption will be violated if the mother is no longer exposed to lead and if the fetal exposure is due to remobilization of lead from the mother's bones. Furthermore, if the mother experiences lead exposures for the first time during pregnancy, the lead will be partitioned among the various body compartments (bone, hair, blood, fetus) in a dynamic manner.

When using PBPK models or other dosimetric adjustments in the risk assessment process for metals, one should explicitly consider the absorption/distribution and kinetic factors discussed above. There are special considerations for cellular uptake, interaction with nutritionally essential and nonessential metal, protein-binding behavior and function, incorporation into bone, metabolism, and excretion as outlined in Table 4-11.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-11. Kinetic factors to consider when evaluating the use of PBPK models or other dosimetric adjustments in the risk assessment process for metals in humans

Cellular uptake	▸ Carrier-mediated uptake (e.g., phosphate or sulfate transporters) ▸ Facilitated transport in the form of organic complexes
Interaction with nutritionally essential and nonessential metal	▸ Competition for binding sites on membrane transport proteins ▸ Interactions at enzyme active sites? ▸ Systemic level interactions altering absorption
Protein-binding behavior and function	▸ Capacity limited to binding to specific proteins ▸ Inducibility of binding proteins ▸ (Zn, Cu, Cd, As, Ni, Hg to metallothionein) ▸ Protein binding as sequestration mechanism ▸ Pb-binding protein in inclusion bodies
Incorporation into bone	▸ Lead sequestered in bone
Metabolism	▸ Relative contribution to overall elimination compared to excretory mechanisms
Excretion	▸ Relative contribution of urinary and biliary excretion ▸ Capacity limitation (saturation kinetics)

Pharmacokinetic models for use in human metal risk assessment incluide three models for lead. The O'Flaherty Model is a PBPK model for children and adults. It includes the movement of lead from exposure media (i.e., intake via ingestion or inhalation) to the lungs and gastrointestinal tract; subsequent exchanges between blood plasma, liver, kidney, and richly and poorly perfused tissues; and excretion from liver and/or kidney (O'Flaherty, 1995). The IEUBK model was developed by EPA for predicting lead levels in children (U.S. EPA, 1994b). The Leggett model allows simulation of lifetime exposures and can be used to predict blood lead concentrations in both children and adults (Leggett, 1993). EPA has a research program for the development of an all ages lead (biokinetic) model and a cadmium biokinetic model based, at least initially, on the Kjellstrom and Nordberg model (Kjellstrom and Nordberg, 1978).

4.2.6.2. *Limitations*

Many of the processes controlling the disposition of metals are intrinsically capacity-limited and highly metal-specific. This makes it necessary to understand physiology well enough to model these processes and methods to estimate binding constants. Another overarching theme is that metal-metal interactions of multiple types (e.g., competition,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

antagonism, and synergism as well as essential-nonessential metal interactions) commonly occur at multiple points during the processes of absorption, distribution, metabolism, and excretion. Another distinctive characteristic of metals is that common sequestration mechanisms, such as incorporation into bone and binding to storage proteins, can result in extended residence times.

In addition to kinetic factors, constructive use of PBPK and PBPD models in the risk assessment process also requires some consensus concerning mode(s) of action and the form of the chemical responsible for the effect of greatest toxicological concern to select an appropriate dose metric. The issue of which endpoints are matched with what form or species of the metal will influence the functional form of the model and hence the dose metric selection. A critical consideration will be to match the toxic endpoint with the active form of the metal in cases where sufficient data exist to suggest that there are one or more active forms of the metal or metalloid (e.g., arsenic).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.3. HUMAN HEALTH EFFECTS

4.3.1. Introduction

Issues of importance when conducting the Effects Assessment (dose-response determination) for human health risk assessments for metals and metal compounds are discussed in this section. The discussion provides some of the scientific basis that underlies metal-specific characteristics of human health effects assessment, but it is not intended to be a comprehensive review. Further detailed discussions on the points raised here can be found in Goyer et al. (2004). Suggested approaches for including metal-specific information in risk assessments are intended to complement other general Agency guidance (e.g., Carcinogen Risk Assessment, Exposure Assessment (U.S. EPA, 2003), Developmental Toxicity (U.S. EPA, 1991).

4.3.2. Essentiality Versus Toxicity

Seven elements are designated as nutritionally essential for humans by the National Academy of Sciences (NAS) (Table 4-12, first column). The categorization as an "essential nutrient" includes the identification of Recommended Dietary Allowances (RDAs) or Adequate Intakes (AIs) by the Food and Nutrition Board (FNB) of the NAS. The FNB has also examined the possible beneficial effects of other elements (Table 4-12, second column), which have not yet been categorized as essential (or not) (NAS/IOM, 2002). The extent to which these elements can currently be considered beneficial to humans and animals varies and is discussed in Goyer et al. (2004) and in NAS/IOM (2001, 2002).

Table 4-12. Metals classified by their known essentiality

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

[a] Possible beneficial effects in some physiological processes and some species as reviewed by the Food and Nutrition Board (FNB) (NAS/IOM, 2000). Beneficial effects have been posited for other metals but have not been officially reviewed by the FNB.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-12 (third column) also lists some metals of interest to the EPA; the FNB has not yet reviewed their status as essential/beneficial nutrients. This category includes the metals lead, mercury, and cadmium. Dose-response curves for essential elements are shown in Figure 4-4.

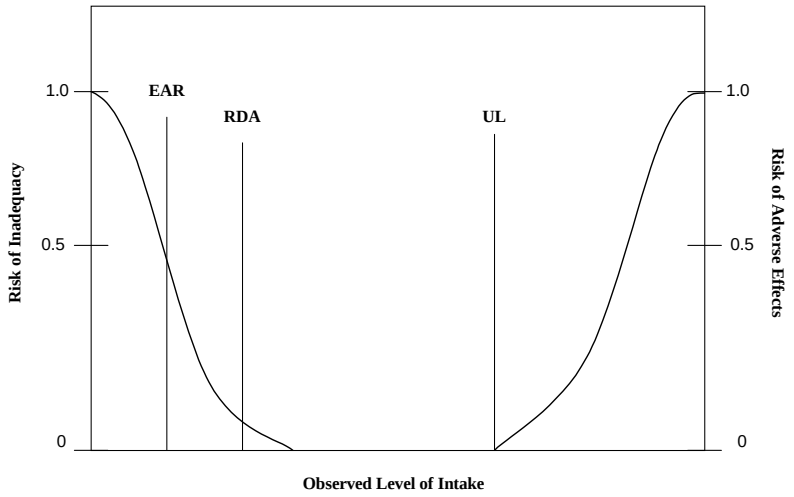

Figure 4-4. Dose-response curves for essential elements. The response of organisms to metals that have both toxic and nutritional properties is conceptualized as having three phases: an area where there is a risk of inadequacy, a neutral area, and an area where there is a risk of adverse effects. Source: FNB (2000)

Note: This figure simply illustrates basic concepts and does not reflect an exact scale. (That is, although it might appear that the RDA is set at a level associated with a risk of inadequacy above 0.02-0.03, that is not the intent.

Dietary Reference Intakes

Recommended Dietary Allowance (RDA)—The average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.

Adequate Intake (AI)—The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; used when an RDA cannot be determined.

Tolerable Upper Intake Level (UL)—The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.

Estimated Average Requirement (EAR)—The average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group**.**

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Considerable concern for human health has been focused on the toxicological aspects of essential metals. Because of this concern, the FNB of NAS has provided Tolerable Upper Level Intake Values and RDAs for these metals where data permit and has provided guidance for assessing risk from dietary exposures to these elements (NAS/IOM, 2001). The World Health Organization (WHO/IPCS, 2002) also has provided guidance on methods for assessing risks from excessive exposure to nutritionally essential metals.

4.3.3. RDAs and RfDs/RfCs

The RDA and Reference Dose (RfD)/Reference Concentration (RfC) differ significantly. The RDA is indexed to a clinical effect of deficiency; and it is used to guide people to take in enough of that material to maintain their health. Conversely, RfDs/RfCs are used to assess the potential for toxic effects from elevated exposures (note that RfDs/RfCs are based on many endpoints, which have differing levels of relevance to whole organism effects). In any case, the RDA is designed to minimize adverse effects associated with nutritional deficiency, so is applicable only to dietary exposures (notably food and beverages). Note that these values are not necessarily synonymous with optimal health (for example, it has been suggested that zinc intakes above the RDA might have certain beneficial/protective effects, including for the prostate in men, for limiting menopausal calcium loss in women, and assisting copper metabolism). RDAs have been identified for different age groups and genders, with RDAs listed for 16 different age-sex and 6 age-pregnancy combinations (NAS/IOM 2003). These RDAs are based on distributions from empirical data or general assumptions that cover 97 to 98% of the population in the given age/gender category, and for women, additional pregnancy/lactational categories. The RDA is given as mass (milligram, or mg) per day.

In contrast, the RfC is used to assess the potential for a noncancer effect. It represents the amount of a given metal or other material that humans can take in every day without appreciable risk of any harmful effect during a lifetime, including for sensitive subpopulations. The RfD is chemical- and route-specific (oral). The RfC represents a similar measure, but for the air concentration to which someone can be exposed (via inhalation). Sensitive subgroups are commonly addressed through the use of uncertainty factors (which also account for variability) incorporated into these values. Dietary exposures to commercial foods (not locally grown) are typically categorized as “background” and are not often included in environmental risk assessments. The The RfD is given as a mass (mg) per kilogram (kg) body weight that can be safely ingested orally every day, and the RfC is given per m^3 of air (i.e., amount safely inhaled).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Both RDAs and RfDs/RfCs have been developed for several metals; for example, values exist for chromium, copper, manganese, molybdenum, selenium, and zinc), and ULs are available for boron and vanadium, and RfDs (but not RDAs) are available for certain compounds of those metals. This highlights the basic concept underlying all of toxicology that *the dose makes the poison* (from Renaissance physician Paracelsus). That is, dose is the key factor in determining whether the effect of a given metal will be beneficial or adverse, considering other exposure conditions.

4.3.4. Biology Relevant to Toxic and Essential Properties of Metals

The bioaccessibility and bioavailability of metals in locally grown food will depend on the species of the metal in the environment and after ingestion; this exposure may be affected by other chemicals such as metal-chelating agents that restrict uptake (e.g., phytates in plant foods) or facilitate uptake (e.g., ascorbic acid). Metals in food can be found in organic forms or complexes not found in soil, sediment, water, or air. For these reasons, the bioavailabilityof a metal within food may differ considerably from its bioaccessibility in an environmental media; to illustrate, different oral RfDs have been developed for cadmium in food and cadmium in water.

The term “molecular or ionic mimicry” has 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. Such interactions play an important role in the health assessment for specific metals. One well-studied example is the replacement of zinc by lead in heme-synthesis, which inhibits the function of heme-synthesizing enzymes (Goyer and Clarkson, 2001).

Single nutrient deficiencies, such as iron deficiency anemia or iodine deficiency goiter, are well characterized. Generally, intake of essential elements is sufficient in affluent populations to avoid such diseases. However, mild multiple nutrient deficiencies may occur that may be indistinguishable from the pathophysiological effects of primary deficiency of a single metal. In conducting environmental exposure analyses, it is important to consider whether any nutritional deficiencies exist in the population being assessed, or if intake of all trace elements needed to maintain health is met, so results do not confuse adverse health effects due to nutritional deficiency with those resulting from toxic responses to excessive levels.

The uptake of essential metals from dietary food and water and their subsequent distribution within the body are regulated by homeostatic mechanisms that allow enhanced absorption or excretion at low dietary intakes and diminished absorption/excretion with high

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

dietary intakes. Furthermore, dietary factors can reduce the uptake of essential metals. For example, high amounts of phytates in the diet complex with endogenous and exogenous zinc, thus preventing reabsorption and increasing zinc elimination. Specialized carrier proteins that may originally have developed as a transfer mechanism for the essential elements also are used to sequester or eliminate nonessential metals (see above, Section 4.3.3.3).

However, homeostatic control mechanisms can be overwhelmed (e.g., by ~~the~~ a high dose level) or otherwise circumvented to produce a toxic effect . (Note that actions of metals on skin or pulmonary membranes are not driven by homeostatic controls.) For example, at high doses chromium salts can produce severe effects in the skin or respiratory tract mucosa, and inhalation of zinc oxide fumes can give rise to inflammatory response (per cytokine excretion) that can produce a local tissue effect (unrelated to systemic zinc exposure levels)..

Toxic effects of metals also result from interactions that block the availability or activity of essential metals. For example, lead can block the utilization of iron in heme synthesis by inhibiting the enzyme ferrochelatase, and there is evidence that cadmium can block the entry of zinc into the fetus, thereby causing a variety of developmental defects in the newborn. Cadmium, lead, and mercury, in combinations or by themselves, may reduce the availability of zinc, copper, and selenium when these essential elements are present in marginal amounts in the diet. In addition, a competitive interaction between one or more essential metals could lead to toxic effects, e.g., copper toxicity may be enhanced by reduced levels of molybdenum or vice versa.

4.3.4.1. *Limitations*

The RDAs have been developed for essential metals (as well as other materials, including vitamins) and are designed to provide adequate nutritional intake for 97 to 98% of the population. Should there be a narrow window between the required and toxic amounts of an element (e.g., as for selenium), then it is possible that sufficient amounts for those who need the most may be above toxic levels for the majority of the population. This potentiality should be evaluated on a case-by-case basis using what is known about potential sensitivities to that element. As a note, RDAs have been established for single chemicals, not mixtures, while metal RfDs to date are also for single chemicals. Under this situation, the component-based approach to assess mixtures is commonly applied (see section 4.3.6).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.3.5. Toxicity

Metals are associated with numerous health effects that are reviewed in detail in reports from EPA (IRIS reports), the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, reports from the World Health Organization's International Programme for Chemical Safety, and toxicology textbooks. At least five transition metals—arsenic, cadmium, chromium(VI), beryllium, and nickel—are accepted as human carcinogens in one form or another or in particular routes of exposure (NTP, 2002), and inorganic lead compounds are considered probable human carcinogens by EPA's IRIS program, while IARC (2004) has concluded 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 effects of metals are also well documented, including effects on the neurological, cardiovascular, hematological, gastrointestinal, musculoskeletal, immunological, and epidermal systems. For example, following oral exposure, beryllium can cause intestinal lesions and copper can cause intestinal irritation, while nickel can decrease kidney weight and cadmium can cause proteinuria, and both trivalent chromium and nickel can decrease liver and spleen weights. Many metals, including those that are toxic (including carcinogenic), follow the metabolic pathways of similar essential metals, the result of similar binding preferences among various metals (Clarkson, 1986). Carcinogenic metals typically do not require bioactivation, at least not in the sense that an organic molecule undergoes enzymatic modification that produces a reactive chemical species (Waalkes, 1995). Enzymatic modification is generally not a mechanism available for detoxify metals. The body may use other detoxification mechanisms, such as long-term storage (e.g., cadmium) and biliary and/or urinary excretion.

4.3.5.1. *Application*

Many factors related to pharmacokinetics and susceptibility act as determinants of toxicity following exposure to a metal. 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 hematopoetic systems. Survivors of acute high-dose arsenic 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

not usually produce overt gastrointestinal symptoms. For example, low-level, long-term exposure to cadmium in food—sometimes combined with inhalation exposure from cigarette smoking—will cause cadmium 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).

Nickel and nickel compounds and chromium and chromium compounds are well-established contact allergens. Other metals that have been cited as contact allergens include copper (WHO/IPCS, 1998), cobalt salts (AIHA, 2003), organomercurials (AIHA, 2003), beryllium (WHO/IPCS, 1990b), palladium (Kimber and Basketter, 1996), and gold (Kimber and Basketter, 1996). Toxic interactions with the immune system that result in exaggerated responses are known as hypersensitivity or allergic reactions. Allergic contact dermatitis (or delayed hypersensitivity) is one such example and occurs as a result of allergy to a substance (antigen) through cell-mediated immunity. In sensitized persons, such reactions can be provoked by minute amounts of the allergen. There are two main phases in cell-mediated immunity, the sensitization phase (in which the person becomes allergic to the antigen) and the elicitation phase. Sensitization usually takes at least 10 days. When sensitization has been achieved and the individual is then re-exposed, a reaction is obvious after a characteristic delay of 12–48 hours (hence the term "delayed") (AIHA, 2003). 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.

4.3.6. Metal Mixtures

Metal mixtures present interesting challenges for the risk assessor. As described below, certain metals can mimic other metals, and depending on the dose and composition of other the metal mixture can result in either a toxic or protective effect. Because metals are naturally occurring substances, they more frequently occur as mixtures than as single, toxic-level exposures. Thus, it is important to account for multiple, simultaneous metal exposures to realistically assess health risks.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.3.6.1. *Molecular or Ionic Mimicry*

A large body of literature provides examples of *molecular* or *ionic mimicry* of metals. This phenomenon is central to aspects of uptake and biokinetics for metals within the body. The term *molecular* or *ionic mimicry* has 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. A number of reviews discuss this phenomenon, giving examples of the mechanism of toxicity for specific metals (Ballatori, 2002; Clarkson, 1993). Most of these examples involve replacement of an essential metal with a nonessential metal, and *molecular* or *ionic mimicry* may be viewed as a form of metal-metal interaction. For example, the protective effects of zinc against copper toxicity are most likely due to diminished gastrointestinal uptake of copper. Lead replaces zinc in heme synthesis by inhibiting the function of heme-synthesizing enzymes (Goyer and Clarkson, 2001). The substitution of calcium by lead results in toxicity of several vital enzyme systems in the central nervous system. This toxicity impaired the development and function of enzymes involved in the production and transport of neurotransmitters (NAS/NRC, 1993). The uptake of lead from the gastrointestinal tract likely occurs via both passive diffusion processes and via active transport mechanisms used in the uptake of essential minerals such as calcium. Calcium deficiency increases the uptake of lead into the body, presumably as a result of lead uptake via calcium active transport processes. Calcium supplementation then diminish lead uptake via both competitive binding to uptake proteins and down-modulation of active transport activity. Lead is actively taken up into the body and sequestered into bone because of ionic mimicry for calcium. Similarly, cadmium uptake may in large part be related to ionic mimicry of zinc. Divalent inorganic mercury forms linear bonds that form a complex that structurally mimics oxidized glutathione. Arsenate complexes with phosphate in the sodium-dependent transport system in renal cells, and the arsenate replace the phosphate in mitochondria, impairing synthesis of ATP and energy metabolism.

As a converse of the enhanced toxicity that can result from nutritional deficiency, the effects of moderate doses of naturally occurring metals that are not required for nutrition can be reduced (or antagonized) by essential metals found in foods. Diet, therefore, can be a major factor in determining whether potential adverse health effects of additional metal exposures are moderated or enhanced . For example, humans can be exposed to mercury by consuming fish that have absorbed mercury from contaminated water, whereas selenium present in the same water can act as a natural antagonist for mercury toxicity, and vice versa (although the protection is inferred through formation of non-reactive mercury-selenide complexes, rather than as result

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of ionic mimicry); cadmium in soil can be ingested via fruits and vegetables grown on that soil, while zinc in nuts also eaten as part of that diet can limit (or antagonize) cadmium toxicity. Relative intakes of zinc, sulfur, or iron play a significant role in modulating copper deficiency or toxicity. Suttle and Mills (1966) showed that dietary levels of copper at 425 mg/kg caused severe toxicosis in pigs. However, all signs of toxicity were prevented by simultaneously supplementing the diet with 150 mg/kg zinc and 150 mg/kg iron.

4.3.6.2. *Studies of Metal Mixtures*

Few controlled studies exist on the toxicologic interactions of metals relevant to levels found in the environment. ATSDR has compiled and evaluated interaction studies for various combination of chemicals, including two sets consisting only of metals: (1) arsenic, cadmium, chromium, and lead; and (2) copper, lead, manganese, and zinc. Additional interaction profiles that include two or more metals are: (3) cesium, cobalt, strontium, trichloroethylene (TCE), and polychlorinated biphenyls (PCBs), and (4) arsenic, strontium-90, TCE, hydrazine, and jet fuels (available online at http://www.atsdr.cdc.gov/iphome.html). Few studies quantified the magnitude of the interaction, whether using the authors' definitions of toxicologic interaction or EPA's definitions based on dose and response addition. (This same limitation also applies to non-metal mixtures.) The summaries below indicate some of the qualitative conclusions available regarding potential toxic interactions.

A study of a mixture of cadmium, lead, and zinc study in rats found slightly more marked adverse hematological effects with the ternary mixture exposure than with the cadmium-lead, cadmium-zinc, or lead-zinc mixtures (Thawley et al., 1977); inconsistencies in dietary levels of calcium and vitamin D in this study, however, may have made comparisons problematic. A well-controlled rat study has reported significant synergism between cadmium and lead regarding testicular atrophy (Saxena et al., 1989). That study also demonstrated protective effects of high dietary levels of zinc, which effectively reduced the testicular effects of the cadmium-lead mixture to control levels. No studies have been located that would allow extrapolation of those high exposure results to more common, lower environmental levels. Fowler and Mahaffey (1978) investigated a relatively wide range of endpoints in studies that covered each metal singly and all possible binary and ternary mixtures. Body weight gain was depressed equally by the ternary mixture and the cadmium-lead mixture, and to a lesser extent by the arsenic-lead and cadmium-lead mixtures, whereas food utilization was depressed more by the ternary and arsenic-cadmium mixtures than by the other binary mixtures. In general, the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

biological parameters studied in this report indicated changes of smaller magnitude and inconsistency in direction for binary mixtures compared with ternary mixtures.

For some endpoints, the data are not sufficiently robust to show even the direction of interaction (i.e., whether the joint action will be dose additive or greater or less than additive). Many animal studies use commercial diets or semi-purified diets that may have higher or lower levels of essential metals than human diets. Much higher doses of the metals appear to be required to elicit effects when commercial diets are used than when semi-purified diets are used. At the other extreme, effects are seen at very low doses when deficient diets are used. Comparisons among studies are therefore problematic, particularly when the diets are not specified. Experimental efforts to identify and quantify interaction mechanisms among metals are still needed.

4.3.6.3. *Human Health Assessment*

Approaches for assessing joint toxicity following exposure to mixtures have been developed by EPA (U.S. EPA, 2000b, which updates U.S. EPA, 1986a). The selection of risk assessment approach begins with the assessment of data quality. Available data are classified into three categories: data on the mixture of concern, data on a mixture of a toxicologically similar nature, and data on individual effects of each component chemical in the mixture. The first approach—assessment of the data based on the mixture of concern—is the preferred approach when the data allow and is essential when considering a complex mixture (e.g., containing hundreds of component chemicals). Such data include epidemiologic studies on the complex mixture or in vitro data on the complex mixture. The typical example of a complex mixture is coke oven emissions; few metal mixtures relevant to environmental exposures would be expected to fall within this category. The second approach is an assessment of data on a mixture of a toxicologically similar nature to that of the mixture of concern, and a similar limitation applies to the usefulness of this approach. The third approach is based on the toxic or carcinogenic properties of the components in the mixture. In this approach, information on toxicologic interactions of components is incorporated into the assessment. This last approach will likely be most useful for assessing metals in the environment, because this situation is most common (i.e., something is known about the components of the mixture but nothing is known about the mixture itself, or a similar mixture).

When no information on interactions exists (i.e., to indicate higher-than-additive or lower-than-additive results), a dose-additive or risk-additive model is applied as a default. The decision on which of these to use depends primarily on how toxicologically similar the metals in

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the mixture are. For metal mixtures, a dose-additive approach would be suggested if each metal could be thought of as a concentration or dilution of every other metal in the mixture. Three approaches have been used when the components are considered to be dose additive: the Hazard Index, the Relative Potency Factors, and the Toxicity Equivalence Factors (a special case of the Relative Potency Factors). The choice of approach will depend on the quality of the data. If the metals were assumed to behave independently of each other, then response addition would be the approach applied. This approach is often used for cancer assessments at Superfund sites and other environmental contamination situations; note that response addition is not valid for high exposure concentrations. For mixtures containing metals known to interact, then an interaction-based Hazard Index can be estimated (U.S. EPA, 2000b; Hertzberg et al., 1999).

Dietary information is an important part of evaluating the potential for mixture toxicity and interactions. As described above, some quantitative data exist for some metal combinations, and where sufficient data exist, they can be used to predict the pattern of interactions for various proportions of the mixture components or to quantitatively modify the risk assessment. Although at this time few such data are available, some studies do exist, and in some cases the results can offer at least qualitative insights. For example, *in-vitro* studies showed that chromosome mutagenicity resulting from co-exposure to arsenic and antimony was less-than-additive. That is, less cell damage was observed than would have been expected from an additive effect from the two metals (Gerbel, 1998). However, it may be difficult to validate laboratory data in the absence of comparable field (epidemiological) data (McCarty et al., 2004). Exposures to other types of stressors also must be considered. A recent progress report on a mixtures study of metals and polycyclic aromatic hydrocarbons (PAHs) indicated that environmental metals decreased levels of the enzyme needed to catalyze PAH bioactivation (a precondition of carcinogenesis), affecting induction at both transcriptional and post-translational levels (Kaminsky et al., 2003). (Note that the carcinogenicity of the metals themselves has not yet been assessed.)

A number of in vivo studies of multiple metals and metal compounds were published before 1980. The draft interaction profiles developed by the Agency for Toxic Substances and Disease Registry and EPA include evaluations of these metals and more recent publications for a selected set of metals.

The EPA provisional interaction profile for arsenic, cadmium, lead, and zinc includes information relevant to chronic exposures as well as insights from acute toxicity studies. Some acute studies considered a variety of endpoints – mortality, testicular necrosis, and hepatotoxicity (Hochadel and Waalkes, 1997) – while others focused only on mortality (Yanez et

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

al., 1991; Diaz-Barriga et al., 1990; Yoshikawa and Ohta, 1982). The studies captured in these draft profiles often include measurements of changes in chemical distributions in target tissues, which can be difficult to interpret in terms of potential health risks. Nevertheless, some specific joint toxicity insights can be gained. An example of how this information can be summarized for at least qualitative consideration in a health risk assessments is given in Table 4-13.

Current studies of toxicological interactions are limited, often relying on in vitro assays of bacteria and cell lines. These studies have tended to focus on mechanisms at the cellular and molecular levels, although their implications for health risk assessment on the tissue or whole organism level are not yet clear. For example, Pounds et al. (2004) identified responses in a recent study of interaction toxicity among simple chemical mixtures of cadmium, mercury, methylmercury, and trimethyltin, using cultured murine renal cortical cells that are targets for metal toxicity. Meanwhile, a model for synergistic metal activation leading to oxidative damage of DNA (genetic material, deoxyribonucleic acid) has been developed by Sugden et al. (2004). This model used in vitro assays to assess the oxidative activation of chromate by arsenite. Although toxicokinetics are a common focus of recent work, interesting new studies are also breaking ground in the area of toxicodynamics, including those under way at TNO in the Netherlands (by J. Groten and collaborators). Future studies are expected to produce key insights that will improve the ability to assess human health implications of exposures to multiple metals.

4.3.7. Variations in Susceptibility

Many factors can contribute to human variation in susceptibility to metals. In addition to diet/nutritional status discussed above, these include other lifestyle factors such as smoking or alcohol consumption. Smoking can damage the lung, which can affect the ability to withstand the insult caused by simultaneously or subsequently inhaling metals, particularly those that act directly on the lung such as beryllium, cadmium, chromium, and nickel. Similarly, alcohol damage to the liver can be exacerbated by metals that also cause liver pathology. Other factors influencing susceptibility include age, gender, concurrent damage or disease, and genetic polymorphisms. The discussion below focuses on susceptibility issues considered key for metals; such issues should be at least qualitatively considered in identifying and evaluating potentially susceptible subpopulations for metals risk assessments. Examples for each of these additional factors are offered below.

4.3.7.1. *Age*

Differences in the pharmacokinetic behavior of metals exist at different life stages,

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

particularly for the nutritionally essential metals (WHO, 1996a). During the immediate postnatal period, absorption of essential metals is poorly regulated (e.g., chromium, iron, zinc) until homeostatic regulatory mechanisms become established with increasing gut maturity. Much of what is known about gastrointestinal absorption during infancy is derived from animal studies; few studies have been conducted on humans. On the other hand, numerous studies have been conducted on the effects of lead and the developing nervous system in humans (IPCS, 1995; NAS/NRC, 1993). It is suspected that the human placenta is resistant to transport of cadmium (Goyer, 1995). It has also been shown that neonate experimental animals have a higher absorption of both lead and cadmium (Kostial et al., 1978). The efficiency of intestinal uptake of some trace metals, particularly zinc, declines in the elderly, but differences between mature adults for other metals of interest to EPA were not identified in a study conducted several years ago (WHO, 1996c). For comparison, the RDA for copper for children up to 8 years old is just under half that identified for teenagers to adults (NAS, 2001).

The sensitivity to skin irritants is considered to generally decrease with age, so children could be more sensitive to metal irritants. Meanwhile, the general loss of renal function with age means older adults will be less able to withstand the harmful effects of metals that affect the kidney, (e.g., cadmium; U.S. EPA, 1999). Note that the RDAs specifically tabulated for older adults (FIU 2004) remains similar to those identified by NAS for this population group within the overall tables published in 2001 (FIU 2004). Thus, when assessing metal risks across different population groups, it will be important to review the current status of metal-specific information with age implications for the metal(s) in that study.

4.3.7.2. *Gender*

Pregnancy and lactation increase demand for some essential metals, particularly copper, zinc, and iron (NAS/IOM, 2003; Picciano, 1996). Because of physiological changes that include higher iron (and calcium) requirements, hormonal changes, and susceptibility to respiratory disease, it has been suggested that pregnant women could be predisposed to the toxic effects of beryllium, lead, and manganese (U.S. EPA, 1999f). As a note, the RDAs for copper, iron, molybdenum, and selenium are higher for pregnant and lactating women than for other women or men; for selenium, the RDA for other women is the same as that for men (NAS/NRC, 2000); in contrast, the RDA for zinc is the same for pregnant women 19 to 50 years old as it is for men aged 19 to 70 and older. For additional comparison, the RDA for chromium for pregnant women is roughly the same as that for men, which is higher than for non-pregnant women and lower than for lactating women (NAS/NRC, 2001).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

References to women as being highly susceptible to metal toxicity usually refer to effects on the fetus during pregnancy (e.g., of lead and mercury), but basic gender differences independent of pregnancy also may account for differences in toxicokinetics between women and men. Women have only about two-thirds the fat-free body mass of men—so their protein and energy requirements are lower—while having a larger percentage of body fat. The male/female ratio for urinary creatinine excretion (an index of body muscle mass) is 1.5. Men are generally larger than women. Skeletal size as well as body calcium are a function of height, and calcium can also be lost as women age. These differences have an impact on body content of minerals (WHO/IPCS, 2002). Women also have significant loss of iron during menstruation, and it has been shown that absorption and toxicity of cadmium are greater in women, related to decrease in iron stores (Berglund et al., 1994).

4.3.7.3 *Concurrent Damage or Disease*

People with higher-than-average biological sensitivity to environmental stressors include allergics and those with pre-existing medical conditions (e.g., with compromised immune systems as a result of a disease or treatment for it, such as chemotherapy). For example, chemotherapy can damage the kidney over time, and at certain levels other medicines (such as acetaminophen) can damage the liver. This may increase metal sensitivity for those metals that cause liver dysfunction.

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). For example, both nickel and chromium can cause allergic contact dermatitis, so their combined presence could result in joint toxicity with a potential for interaction; broken skin could potentially increase the absorption of other metals (and other toxic agents) across the exchange boundary. Beyond these well-established contact allergens, other metals have also been cited as possible contact allergens, including copper (WHO/IPCS, 1998), cobalt salts (AIHA, 2003), beryllium (WHO/IPCS, 1990b), palladium (Kimber and Basketter, 1996), and gold (Kimber and Basketter, 1996).

With regard to effects associated with high-dose metals exposures, elevated arsenic intakes – from drinking water with levels 17 times above the U.S. drinking water standard – have been linked to blackfoot disease, a vascular complication that represents a severe form of arteriosclerosis (EPA 2004). like many such diseases, the incidence of blackfoot increases with age and thus is also linked to the age factor. Some studies suggest that higher doses of copper and manganese might be linked with Parkinsonism (which could be reversible) (Feldman, 1992;

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Gorell et al., 1999). Thus, these studies offer insights for specific metals risk assessments where exposure conditions, including levels and durations, were sufficiently similar.

4.3.7.4. *Genetic Polymorphisms*

Individuals vary considerably in the nature and severity of their response, and potential repair and recovery, from exposure to metals and metal compounds. Such differences may be due to genetic polymorphisms that can alter the transport and metabolism of a metal. The most apparent of these genetic polymorphisms affecting metabolism and toxicity of metals are disorders in homeostatic mechanisms for nutritionally essential metals.

Two disorders affect copper metabolism: Wilson disease and Menkes disease. Wilson disease is an autosomal recessive abnormality (prevalence of 1 in 30,000) that is believed to be due to impaired biliary excretion of copper, resulting in accumulation in and damage of various tissues, particularly the liver, brain, kidney, and cornea; hemolytic anemia can also result. Menkes disease is an X-linked recessive disorder of copper metabolism (prevalence of 1 in 200,000) that resembles copper deficiency regardless of level of copper intake (WHO/IPCS, 2002).

Hemochromatosis is a common inherited disorder related to iron homeostasis. This disorder is characterized by excessive iron absorption, elevated plasma iron concentration, and altered distribution of iron stores (altered iron kinetics). One long-term effect is liver cirrhosis, with increased risk of liver cancer (NAS/IOM, 2003).

ATSDR (2003) reported that a relationship between human leukocyte antigens (HLA)[1] and nickel sensitivity was observed in patients who had a contact allergy and positive results in a patch test for nickel. The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen compared with normal controls. The relative risk for patients with DRw6 to develop a sensitivity to nickel was approximately 11-fold.

A genetic polymorphism for a heme-metabolizing enzyme affecting lead metabolism was identified in 1973 (Granick et al., 1973), but the molecular characteristics and potential clinical implications did not receive attention until about ten years ago (Smith et al., 1995). Fleming et al. (1998) found that the relationship of bone lead to the cumulative blood index for workers

[1] 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

with occupational exposure was greater in those workers with the ALAD1 allele, suggesting that the ALAD2 genotype decreased transfer of lead from blood to bone. This effect was only demonstrated in workers with higher blood lead levels than the general population.

It is suspected that genetic polymorphisms also exist for arsenic metabolism (NAS/NRC, 2001), but these have not yet been defined. Other genetic polymorphisms that may affect the metabolism of chemicals continue to be described. The human MT gene locus is very complex; four individual isoforms and more than ten subforms of the MT1 gene exist, including functional and nonfunctional genes. Because of the protective role that MT plays in metal metabolism, an understanding of the biological role of significant variations in this MT gene locus (both within and among individuals) can offer insights into differential sensitivity or susceptibility and will help characterize variability across a population.

Although all MT proteins are associated in some way with a protective role, each of the multiple isoforms appears to have a unique function, as reflected by their unique tissue distributions, the specific conditions under which each is expressed, and unique properties of the metal binding clusters (Bogumail et al., 1998). The multiplicity of the human MT gene loci makes them potentially important for understanding genetic variability. Emerging technologies are enabling new research in the areas of genomics, proteomics, and metabolomics that will eventually improve human health risk assessments for metals and other stressors, including the role that MT isoforms play in variability in response.

Other creative approaches have coupled human tissue studies with animal toxicology studies. For example, studying lung slices from humans (from transplant or tumor resection) and from rodents exposed to the same metals offers promise for improving our understanding of potential effects from inhalation exposures. Comparison of study results between rats and mice under similar exposure regimes and linking them to similar human exposures will provide insights into whether human responses are better predicted by rats or by mice.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.4. ECOLOGICAL EXPOSURE PATHWAY ANALYSIS

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

Exposure routes include inhalation, ingestion, and dermal or, for plants, root uptake and leaf exposures. *Pathways* describe the specifics of any exposure and include transport of the contaminant in the environment as well as exposure route for organisms of concern (e.g., dietary ingestion of a soil contaminant that has been taken up by plants). *Phase association* and *chemical speciation* influence metal movement through pathways and the availability of a metal for delivery of the dose to receptors of concern.

Metal Exposure Assessment

Metal exposure assessment includes consideration 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.

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

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

Methods for assessing transport of metals through various media (water, soil, air) are described in this section. Exposure to aquatic organisms through water and dietary routes (looking again at models to account for site-specific differences in bioavailability) is also

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

discussed. The section concludes with discussions about quantifying exposure to metals for terrestrial organisms.

4.4.1. 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 usel 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 an optimal remediation strategy can be developed.

Although numerous models are available for use, most are based on the same fundamental principles. That is, metals are ubiquitous in the environment, as they are found in the aquatic, terrestrial, and atmospheric compartments. 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, as well as the movement (i.e., the transport) of each of these within and among the various compartments. It is important 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. Note that it is not necessary to include all of the compartments in every model. 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 features included 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 is 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, and that the analyst also must possess a relatively high level of modeling expertise. 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 germane 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.

An overview of some of the aquatic fate and transport models available for use is presented in the following subsection. Although models that include some metal-specific capabilities will be noted, no single model that is currently available for use includes all of the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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., see the discussion of the Unit World model in Section 5). As a result, metal fate and transport models should be viewed as an evolving technology, with new models expected to become available in the not too distant future.

4.4.1.1. *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 4-5). The analyst has the option of using independent hydrodynamic transport, sediment transport and chemical fate models, or an integrated model that incorporates all of these processes. Although the models described below are mainly in the latter category, their use does not preclude the use of a stand-alone model (e.g., a hydrodynamic or sediment transport model) as an aid in the development of inputs to the integrated model.

Modeling the movement of metals through an aquatic system begins with a characterization of the movement of water 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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

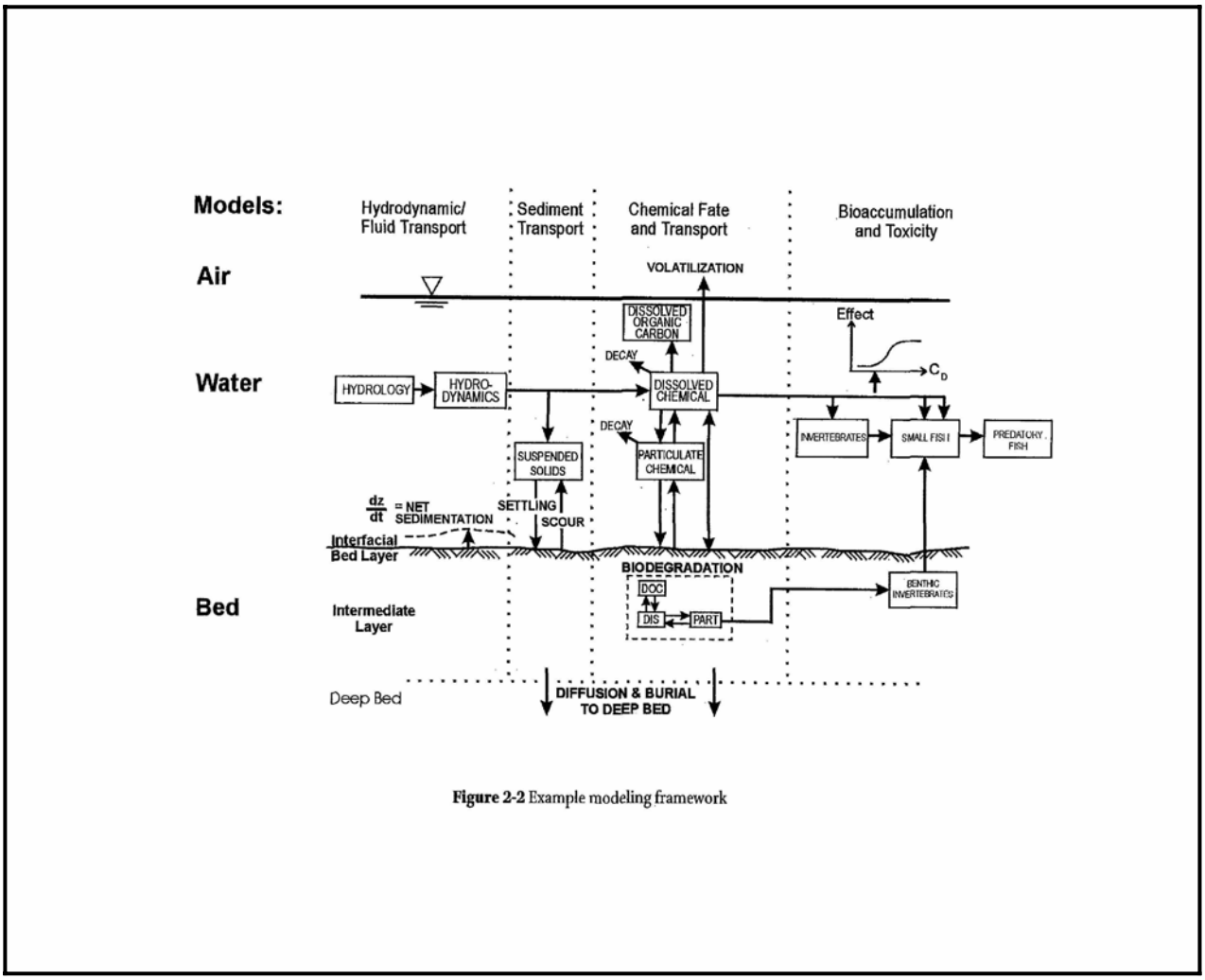

Figure 2-2 Example modeling framework

Figure 4-5. A generalized model framework for chemical fate and transport in an aquatic system.

Source: Paquin et al., 2003.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The reader 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 U.S. 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.

4.4.1.1.1. ***Applications.*** As noted above, 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 analyst'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

Integrated Model

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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 fate and transport models that may be considered for use in the analysis of an aquatic setting are listed in Table 4-13 and discussed below. The models range in complexity from simple mass-balance calculations that can be performed on a hand calculator, to one-dimensional steady-state models, to multidimensional time-variable models. The models are listed in groups that correspond to the mathematical solution technique used to solve the governing mass-balance equations (analytical solution, steady-state numerical solution, and time-variable numerical solution), a categorization that is approximately in accordance with their ease of use as well. Paquin et al. (2003) describe example applications of many of these models to illustrate how they have been previously applied. Although publications of successful modeling applications serve as useful illustrations of how models may be used, it is important to bear in mind that "past performance should not be viewed as a promise of future returns." That is, the successful application of any model will depend on many factors other than the model framework itself, including the complexity of the problem setting, the data that available for use, and the experience of the analyst. Another important point to keep in mind is that a complicated model is not necessarily a "better" model to use than a simple one. Models should be selected on a case-by-case basis.

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.

The simplest modeling analysis to consider involves simple screening-level calculations. While clearly applicable to a screening level of analysis, such calculations can frequently provide a quantitative perspective on the severity of a problem, one that will be useful in defining the nature of subsequent modeling analyses that may be required.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-13. List of fate and transport models

Abbreviation	Name	References
Analytical Solution Models:		
WQAM	Water Quality Assessment Methodology	Mills et al. (1985, 1982a, b)
DJOC-III	Donald J. O'Connor (1988), a triad of papers	O'Connor (1988)
RIVRISK	RIVer RISK	Grieb (1995); EPRI (1996)
SLSA	Simplified Lake and Stream Analysis	Di Toro et al. (1981) HydroQual (1982)
USES	Uniform System for Evaluation of Substances	RIVM et al. (1994), as described in Johnson and Luttik (1995)
QWASI	Quantitative Water Air Sediment Interaction	Mackay (1991); Mackay et al. (1983)
TRANSPEC	Transport and Speciation	Bhavsar et al. (2004**)**
Steady-State Numerical Solution Models:		
CTAP	Chemical Transport and Analysis Program	HydroQual (1982, 1981)
PAWTOXIC	PAWtuxent TOXICs	Wright (1987)
SMPTOX3 (Version 2)	Simplified Method Program - Variable - Complexity Stream Toxics Model	LTI (1992) Dilks et al. (1995, 1994)
MEXAMS	Metals EXposure Analysis Modeling System Includes EXAMS and MINTE	Felmy et al. (1984) Burns et al. (1982)
Time-Variable Numerical Solution Models:		
EXAMSII	EXposure Analysis Modeling System - II	Burns and Cline (1985); Burns et al. (1982)
RIVEQLII	RIVEr QuaLity II	Chapman (1982)
WASTOX	Water Quality Analysis Simulation of TOXics	Connolly and Winfield (1984)
RCATOX (AESOP)	Row-Column AESOP for TOXics (Advanced Ecological Systems Operating Program)	HydroQual (2003)
WASP5	Water Quality Analysis Simulation Program, Version 5 Distributed w/ DYNHYD5, Dynamic Hydrodynamics 5	Ambrose et al. (1993) Ambrose et al. (1993)
META4	Metal Exposure and Transformation Assessment Model	Medine (1995) Martin and Medine (1998)
DELFT3D	Delft 3D Model	Delft Hydraulics (1998)
MIKE21	MIKE21	Danish Hydraulic Institute
HSPF	Hydrologic Simulation Program - FORTRAN	Bicknell et al. (1993)
RECOVERY	RECOVERY	Boyer et al. (1994) Ruiz et al. (2000)
EFDC	Environmental Fluid Dynamics Code	Hamrick (2002)

Source: Paquin et al. (2003)**.**

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Water Quality Assessment Methodology (WQAM) is an excellent resource for use in these types of analyses. WQAM describes a variety of simple screening-level procedures that may be used in water quality assessments. It provides a useful overview of the types of simplified analyses that may be performed and is a generic framework that does not generally attempt to address metal-specific modeling needs. An analyst having limited water quality modeling experience would probably find this to be a useful reference.

A series of three papers by O'Connor (1988) also provide a helpful introduction to the basic concepts and use of fate and transport models. These publications include analytical solutions and example applications for a variety of conditions, including spatially varying suspended solids concentrations. Although these solutions are not currently available in the form of a computer program, they could be readily adapted for this purpose.

Analytical solution models tend to be inherently simple models, a requirement of the solution technique used. As a result, they tend to have modest development and computational requirements (an advantage), but, at the same time, they limit the analyst with regard to the level of detail that can be used to represent the problem setting with the model. For example, these models normally allow the user to represent the system as a one-dimensional, uniform cross-section stream or a completely mixed water body, with constant inputs over time, and particulate and dissolved exchange of chemicals between the water column and sediment. Their simple structure makes these models well suited for use in screening level analyses. Models in this category include the River Risk (RIVRISK) model, Simplified Lake and Stream analysis (SLSA) model, and Uniform System for the Evaluation of Substances (USES) model. Each of these models includes a water column and a single-layer sediment compartment. RIVRISK is a steady-state model that may be applied to a one- or two-dimensional stream setting. It is one of the few models in Table 4-13 that includes a bioaccumulation subroutine. However, it is a proprietary model of the Electric Power Research Institute and is available only to registered users. The SLSA program (HydroQual, 1982; Di Toro et al., 1981) may be used to represent a one-dimensional stream or a completely mixed lake. Its utility in time-variable mode was demonstrated by its success in simulating the long-term (about 5 years) recovery of a quarry that had been dosed with instantaneous releases of the organic chemicals DDE and lindane (Di Toro and Paquin, 1984). Finally, the USES model was developed in Europe to model dissolution and movement of antifoulant paints on boats (Johnson and Luttik, 1995). It provides the analyst with a simplified way to estimate concentrations of organic chemicals and metals in a completely mixed water body, with successful model applications having been reported for metals (Johnson

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

and Luttik, 1995). USES has recently been replaced by a considerably more complex version, the European Union System for the Evaluation of Substances (EUSES) model (Berding et al., 1999).

Another analytical solution model that has been refined to include metal-specific features is the Quantitative Water Air Sediment Interaction (QWASI) model (Mackay, 1991; Mackay et al., 1983). QWASI, developed as a fugacity model for application to lakes and rivers, is used to simulate the exchanges of chemicals with measured vapor pressure between air, water, and sediments (the Unit World Model for organic substances). A numerical solution version was subsequently developed, one that considers multiple species, as occurs with metals (Diamond et al., 1992). More recently, it has been coupled with MINEQL to allow for interconversion of species and consideration of metals in dissolved, colloidal, and particle phases in water. It is known as the TRANSport and SPECiation (TRANSPEC) model (Bhavsar et al., 2004) and is not yet applicable to sediments.

The remainder of the models listed in Table 4-13 and described below are numerical solution models. The first four are applicable to steady-state conditions and the remainder to time-variable conditions. The steady-state models are appropriate for use in a screening level or definitive level of analysis. Their main advantage in comparison to analytical solution models is their capability to represent more complex system geometry and transport regimes (at the expense of an increased level of effort required to set up the model). The Chemical Transport and Analysis Program (CTAP) is essentially a numerical solution version of SLSA, with the added capability of being able to represent two- and three-dimensional systems and multiple-particle size classes. Pawtuxent Toxics (PAWTOXIC) is a relatively simple one-dimensional model for estimating particle deposition or resuspension in river and streams, assuming EqP conditions. PAWTOXIC does not include exchange of dissolved metals between water and sediments, and it can be used only to simulate net settling or resuspension.

The Simplified Method-Program Variable-Complexity Stream Toxics (SMPTOX) is of particular interest for metals because it represents one of the first models to include the simulation of AVS and SEM (see Section 3.4) for copper, cadmium, nickel, lead, and zinc. It does not consider the potential for oxidation of metal sulfides. SMPTOX, another model that has evolved from the SLSA framework, is applicable for use in simulating a one-dimensional river or stream and it also includes both particle settling and resuspension and a diffusive flux of dissolved metals between water column and sediments. As a Windows-based model, it is relatively simple to use.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The last steady-state model to be considered, Metals Exposure Analysis Modeling Systems (MEXAMS), links EXAMS (a widely used fate and transport model developed by EPA) with MINTEQ, a chemical equilibrium model (Felmy et al., 1984) (see Section 4.1, Environmental Chemistry, for further discussion of MINTEQ). MEXAMS has not yet been coupled with EXAMSII (a time-variable model), so it can handle only steady-state conditions. EXAMS can be applied to a one-, two-, or three-dimensional system and includes an interactive bed layer. By transferring total metal concentrations to MINTEQ in an iterative process, EXAMS is able to calculate fate and transport of metal species. It requires the user to specify a bulk exchange coefficient to represent water-sediment exchange.

The remaining models listed in Table 4-13 include the capability to perform time-variable simulations. As a general rule, such models also can be used to simulate steady-state conditions, such as determining simple waste-load allocations during critical low-flow conditions. Input requirements will be relatively high for time-variable models, as the user may need to specify time variable inputs (e.g., upstream and tributary flows and concentrations, point source loads). The Exposure Analysis Modeling System II (EXAMSII, Version 2.97) is a relatively well-known model that was originally developed for steady-state applications. EXAMSII also represents bulk exchange of water and solids between the water column and sediment, rather than separate terms for particulate and diffusive fluxes of metal. It has the advantage of being very flexible with regard to execution of both simplified steady-state assumptions and more realistic (albeit more complex) time-variable analyses. It has also been widely used for many years and is well documented.

River Quality II (RIVEQLII) (Chapman, 1982) was developed specifically for inorganic substances. It incorporates relatively sophisticated chemical equilibrium calculations through linking with MINEQL (Westall et al., 1976) (see Section 4.1.5.1 for further discussion of MINEQL). RIVEQLII is applicable to one-dimensional rivers and streams. It assumes equilibrium conditions and incorporates particle setting to the bed, sorption reactions, and precipitation and dissolution of chemical to and from the sediment bed.

The next four models listed in Table 4-13, WASTOX, RCATOX, WASP5, and META4, evolved from an earlier model, the Water Quality Analysis Simulation Program (WASP) (DiToro et al., 1981). The Water Quality Analysis Simulation of Toxics (WASTOX) (Connolly and Winfield, 1984) incorporates particulate and dissolved transport processes that are very similar to SLSA and CTAP. Row-Column AESOP for Toxics (RCATOX) (HydroQual Inc., 2003) is a more recent implementation of WASTOX, one that has the potential to take advantage

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of parallel processing capabilities. Since RCATOX is still under development, it has not yet been released for general use.

The Water Quality Analysis Simulation Program, Version 5 (WASP5) (Ambrose et al., 1993) is the version of WASP that is currently supported by EPA. Essentially, WASP5 incorporates many of the EXAMS capabilities, plus refined sediment transport capabilities. WASP5 is distributed with two different subroutines: EUTRO, which is used in eutrophication problems, and TOXI5 for simulating fate and transport. The WASP5 package also includes an associated food chain model. Notably, WASP5 and RCATOX are designed to interface with state-of-the-art hydrodynamic and/or sediment transport models, a feature not shared by any of the other available fate and transport models. This capability would be of use in estuarine and coastal systems having complex hydrodynamic conditions. WASP5 interfaces with the PC-compatible hydrodynamic model DYNYD5 (Ambrose et al., 1993). WASP5 and RCATOX can both interface with the Estuary, Coastal, Ocean Model (ECOM), a family of hydrodynamic models (Blumberg and Mellor, 1987), and with ECOMSED (HyroQual, 1998), a sediment transport model.

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

The Delft 3D model (DELFT3D), developed by Delft Hydraulics Lab in The Netherlands, is another model that is quite sophisticated with regard to its capabilities. It is a flexible integrated model that includes the following modules: hydrodynamics, water quality (including sediment transport), chemistry, and wave generation. Although the model software is proprietary, the model itself is commercially available.

MIKE21, developed by the Danish Hydraulic Institute (DHI), is another commercially available fate and transport model that is applicable to rivers. This three-dimensional model

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

includes both particulate and dissolved transport processes. One of the modules of a recent release may be used to simulate the fate, transport, and bioaccumulation of metals.

The Hydrologic Simulation Program-FORTRAN (HSPF) (Bicknell et al., 1993) is the most recent version of a family of models originally developed in the 1960s to simulate agricultural runoff. It is unique among the models listed in Table 4-13 because that it includes hydrology and nonpoint-source terrestrial runoff modules, in addition to in-channel fate and transport capabilities. HSPF is frequently used to simulate complex watersheds and provides information for continuous input simulations or for storm events. It models well-mixed reservoirs as well as branched river systems and can include up to three sediment types. It has been widely used throughout the United States, but its high level of sophistication makes it most appropriate for use by experienced modelers.

RECOVERY, a model supported by the U.S. Army Corps of Engineers, has been developed with features that make it amenable to evaluating sediment capping alternatives (Ruiz et al., 2000; Boyer et al., 1994). The model is structured as a well-mixed surface-water layer overlying a vertically stratified but horizontally well-mixed sediment bed. The sediment is defined by three zones (surface, deep contaminated, and deep clean), which can be further subdivided on the basis of porosities, contaminant concentrations, and other factors. RECOVERY is particularly useful for evaluating sediment-capping scenarios and sites with old contamination (where clean sediment has layered over the contaminated bed).

One other model that is nearing release for use as a fate and transport model is the Environmental Fluid Dynamics Code (EFDC) (Hamrick, 2002). EFDC, originally developed as an advanced level hydrodynamic model, was subsequently modified to include sediment transport capabilities. It is a state-of-the-art model that incorporates a variety of options for representing sediment transport. Most recently, it was further refined for use with chemicals, with an initial application to metals in which two-phase linear partitioning was used (Ji et al., 2002); a second application was the ongoing analysis of polychlorinated biphenyls (PCBs) on the Housatonic River in Connecticut. The chemical fate subroutine does not currently evaluate metal speciation. EFDC is scheduled for release in the near future.

Water quality analyses often require probabilistic results, as the WQC in the United States are expressed in probabilistic terms, with an allowable 1-in-3-year exceedance frequency. Steady-state models cannot evaluate a return period for exceedences. When using these models, a Monte Carlo analysis can be conducted to generate a large number of model inputs and subsequent solutions that can then be analyzed probabilistically to obtain a characterization of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

Transport and fate models will vary considerably in their ease of use, with the simpler one-dimensional and analytical solution models placing relatively modest demands on the user. Although it may be a simple matter to set up and run this type of model, their proper use requires the user to exercise a considerable amount of judgment. More complex models become increasingly difficult to use and interpret, and errors associated with setting up the model are not always easy to detect. Hence, it is important that the relatively sophisticated modeling analyses be performed by an experienced analyst, one who is familiar with the details of the processes included in the model being used. Owing to the complexity of setting up and parameterizing the more complex models listed in Table 4-13, particularly for analysis of a complex problem setting, their use will often be limited to relatively refined definitive assessments.

Further detailed discussions about features, limitations, and example applications of the models discussed in this section are provided by Paquin et al. (2003). This review also identifies additional models designed for use in specialized regions of water bodies, such as mixing zones or plumes. The appendix includes information about where to obtain many of models discussed

4.4.1.1.2. ***Limitations.*** 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 4.1.4). It is important for several reasons. First, the distribution of metal between the dissolved and particulate phases has a direct bearing on the magnitude of particulate fluxes of metal that occur in association with the settling and resuspension of sorbed metal. Second, it 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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

affect the metal bioavailability and the route of exposure to a metal (food vs. water). Given its importance, it is necessary to 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 of 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.

For neutral organic chemicals, the magnitude of the partition coefficient is often assumed to be proportional to the dissolved organic carbon content of the particles. Use of linear partition coefficients is likely to be an oversimplification in the case of metals, where a variety of sorption phases may be important. Several models are available that provide a relatively detailed representation of these metal-particle interactions (see Paquin et al., 2003, for a review).

Many models that were initially developed for organic substances assume first-order decay processes. These are of little importance for metals, but they sometimes are used in screening-level assessments to represent removal of sorbed material from the water column. This approach provides a relatively simplistic representation of the underlying processes and should be used with caution. Given the capacity of most computing environments today, the potential exists to use relatively sophisticated metal-specific sorption and water-sediment flux models, even for simple assessments. However, until such subroutines become more widely available, their use will be problematic, especially for an inexperienced user. Modification of existing models may be an option, but this should be attempted only by an individual who is experienced in model development and programming.

Modeling of mercury and metalloids, such as arsenic and selenium, is complicated by transformation processes that change the form of the metal. Methylation of mercury and arsenic or binding of selenium to amino acids (e.g., selenomethioine) changes both their physical and biological properties (see Section 4.1. for a discussion of transformation processes). Similarly, metals that readily change oxidation state (e.g., chromium) also require additional considerations in fate modeling. Many of the same transport models can be used, but input parameters will require modification. Such models are beyond the scope of this framework, which is focused on inorganic forms of metals. See, for example, the Mercury Cycling model by Hudson et al. (1994) for further guidance on fate and transport models for mercury.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

4.4.1.2. *Terrestrial*

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 primarily by leaching into ground water, although in particular instances uptake by plants can represent a significant loss. Section 4.1.4 reviews the processes and models that predict movement of chemicals through soils or partitioning onto mineral surfaces (i.e., partition coefficients). These serve the same role as the fate and transport models discussed above for aquatic systems and therefore are not repeated here.

4.4.2. Routes of Exposure to Aquatic and Terrestrial Species

4.4.2.1. *Aquatic Species*

Potential exposure routes for aquatic species include inhalation/respiration, dermal absorption, and diet (either food or incidental sediment ingestion). The extent to which a metal is taken up by any one of these exposure routes is difficult to define for all relevant routes. Inhalation/respiration, which for aquatic species means general exchange across respiratory surfaces, can involve diverse gill and lung types. Respiratory surfaces include fish gills, various molluscan and arthropod gill types, the pseudo-lungs of pulmonate gastropods, cells surrounding the sponge spongocoel, mammalian and avian lungs, and plant leaves. Absorption includes movement across the skin; the walls of such diverse structures as spongocoels, the cnidarian gastrovascular cavity, and the echinoderm water-vascular system; the filtration-based feeding structures of many crustacea, insects, and polychaetes; diverse phytoplankton cell membranes; and plant roots and leaves. Ingestion pathways can involve direct consumption or consumption after exchange through a trophic web. The diversity of potential receptors makes definition of exposure pathways more difficult for aquatic receptors than for humans.

The respiration/inhalation route is a particular challenge in aquatic exposure assessments because of the differing types of respiratory organs, the dynamic nature of the respiratory process in water, and the intimate contact between a receptor and metals dissolved in waters.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Further complicating the issue, some respiratory organs can also be involved in locomotion, excretion, ion regulation, and food capture, sorting, and ingestion. The absorption route can involve uptake across a phytoplankton cell membrane, amphibian skin, arthropod exoskeleton, the general integument of an infaunal clam or annelid, or the egg membrane of a bird or amphibian. Absorption can occur from overlying or interstitial waters; these sources have very distinct chemistries that influence metal bioavailability.

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

Despite the complexities associated with quantifying exposure of aquatic animals to metals from multiple routes of uptake, the relative importance of the different uptake pathways has received considerable attention in recent years (Wang 2002; Hook and Fisher, 2001; Fisher et al., 1996; Bjerregaard et al., 1985). Bioenergetic-based kinetic models used to describe the accumulation of contaminants in aquatic animals have been developed relatively recently and have been successfully applied to a variety of organic and inorganic contaminants. These models provide a broad framework for addressing controls on contaminant bioaccumulation for diverse organisms and can be used for studying contaminant bioavailability and determining the relative importance of different routes of contaminant accumulation, including that of metals (Landrum et al., 1992; Wang et al., 1996). The models are flexible enough to incorporate environmental variability in contaminant sources, contaminant concentrations, food availability, and organism growth rates in their predictions of organism contaminant levels**.**

Applications of one-compartment biokinetic models using laboratory-based measurements of key model parameters (assimilation efficiency, uptake rates from water and food, elimination rates) have been extended to field situations for populations of marine mussels (Wang et al., 1996; Fisher et al., 1996); Ag, Cd, Co, and Se in clams (Griscom et al., 2002; Luoma et al., 1992); Po in copepods (Stewart and Fisher, 2003; Fisher et al., 2000); Se in fish (Baines et al., 2002); and freshwater mussels (Roditi et al., 2000). 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 to account for the major processes governing contaminant concentrations in aquatic animals and that the laboratory-derived kinetic parameters are applicable to natural conditions.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Temporal aspects of exposure should be considered in assessments of any toxicant. Rapid speciation and phase changes associated with changes in pH/Eh make temporal issues particularly germane to metals. Fluctuating or pulsed exposures occur in situations such as 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 background concentrations but may last for only a few hours. These episodic exposure scenarios have been poorly characterized for metals (Hoang et al., 2005). Any risk assessment for metals should clearly state all assumptions about duration of exposure.

Temporal Aspects of Exposure

Temporal aspects of exposure are important considerations in assessing aquatic risks to metals. Organisms may respond vary different to episodic exposure than they respond to the constant exposures incorporated into classic toxicity bioassays. Sound risk analyses clearly articulate all assumptions about exposure durations.

***Water pathway and respiratory route*.** For acute exposure of most water column organisms, binding of metals to the gill (respiratory) surface is the primary route of exposure. Binding of metals to the gill surface is the primary route of exposure for most water column organisms, at least for short-duration exposures. Chemical kinetics play an important role in this context, as gradients in pH and ionic composition exist at the gill surface microlayer due to respiration, excretion, and ion regulation. Dissolved aluminum toxicity to freshwater fish is a good illustration of this point (Playle and Wood, 1990). The deposition of aluminum on gills is determined largely by the rapid shift from dissolved ionic aluminum to an $Al(OH)_3$ precipitate on the gill surface due to the more alkaline state of gill microlayer water. How much aluminum speciation and phase association changes occur is a function of the initial pH of the bulk water. Exposure assessment should address metal speciation kinetics in such situations (see Section 4.1, Environmental Chemistry) or else inaccuracies will emerge in subsequent effects assessment.

Primary Route of Exposure

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.4.2.1.1. ***Application*****.** Predicting exposure at the respiratory surface should include analysis of chemical speciation, chemical kinetics, and binding with biological ligands on the gill (or equivalent respiratory surface). The FIAM states that, in general, metal ion availability and effect are correlated with free ion concentration or activity in the water (Brown and Markich, 2000; Campbell, 1995). Consequently, knowledge of free ion concentration or activity is crucial to fully describing exposure. The BLM further suggests that the bioactivity of a metal is a result of its interaction with biological ligands (i.e., biological macromolecules on the surface of the respiratory organ) (see Section 4.5, Characterization of Ecological Effects). It follows that a dissolved metal ion's bioactivity is a function of its complexation with dissolved ligands (which determines how much free ion will be available for binding with biological ligands) and the affinity and stability of the metal complexes with the biological ligands. Further complexation of metals takes place within the cells of the respiratory organ, with the remaining free metal available for binding to transport macromolecules for delivery to the organism's circulatory system; this results in the true delivered dose.

Free Ion Activity Model (FIAM)

The ***FIAM*** states that, in general, metal ion availability and effect are correlated with the free ion concentration or activity in the water. It also recognizes the role of competing ions in reducing metal bioavailability (e.g., calcium reducing zinc bioavailability). The FIAM is a powerful tool as long as it is applied with enough understanding to anticipate or recognize exceptions.

Equilibrium speciation can be used to estimate the aquatic free ion concentration and its resulting activity. In some cases, the free ion can be measured directly during an exposure assessment. Combining insights from the FIAM approach with those from the BLM and HSAB (see Section 4.1, Environmental Chemistry) theories allows general prediction of metal activity on biological surfaces as different as fish gills (Janes and Playle, 1995; Reid and McDonald, 1991; Pagenkopf, 1983), green algae (Parent and Campbell, 1994; Crist et al., 1988), and bacteria (Azenha et al., 1995). Entry across the integument could also be addressed with conceptual tools of the FIAM and BLM (Krantzberg and Stokes, 1988), but this application is not yet sufficiently developed for immediate use.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

4.4.2.1.2. ***Limitations.*** The FIAM is a powerful tool as long as it is applied with enough understanding to anticipate or recognize exceptions. As examples of important exceptions, charged uranium complexes are toxic, in addition to the free ion (Markich et al., 2000), and the neutral mercury complex $HgCl_2^0$ is bioavailable due to its high lipophilicity (Simkiss, 1996). Small organic ligands bind metals forming nonionic complexes that are also exceptions to the FIAM. Copper bound to ascorbate was bioavailable to the green alga, *Scendesmus sp.* (Campbell, 1995). Silver bound to glutathione or cysteine was bioavailable to *Ceriodaphnia dubia* (Bielmyer et al., 2002). In addition, some nonionic metal-inorganic ligand compexes, such as NiCO3, may also be bioavailable (Hoang et al., 2004).

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

4.4.2.2. ***Food Chain Pathway and Dietary Exposure***

Defining the particulars of metal exposure by ingestion is complicated by the diversity of feeding modes, digestive systems, and physiology of candidate receptors. That dietborne exposure to metals can result in accumulation in aquatic organisms is well established, although the rate and magnitude vary among organisms. What is less well understood is how best to express dietary exposure in a way that can be linked to potentially toxic effects. For nonionic organic chemicals, evidence is strong that whole-body burdens of chemical (normalized to lipid

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

content) are robust metrics of toxicological dose, and these relationships appear to be independent of whether exposure was via water or diet. In fact, the greatest strength of the body residue approach for organic chemicals is that it effectively integrates different exposure pathways into a single expression of dose and toxicological potency.

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

Although these issues confound the development of simple dose/effect metrics based on whole-body metal residues, one should presume that residue/effect relationships could be established if there were better understanding of more specific concentration/response relationships for the site (or tissue) of toxic action. For example, some studies have suggested that the metal concentration in the cellular cytosol (as opposed to that bound to cell walls or sequestered in nonbioavailable metal granules) may provide a better expression of internal metal dose associated with toxic effects (Wallace and Luoma, 2003; Wallace et al., 2003; Wallace and Lopez, 1996). Others have suggested that whole-body residue residue-effect 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, and, therefore, effects are governed by factors that influence the rate of uptake. When uptake 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).

Assessment of dietborne metal exposure is best considered 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.

For these reasons, assessment of dietborne metal exposure should be considered in two contexts: (1) dietborne exposure leading to accumulation and exposure to higher trophic levels

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

in the food chain (e.g., humans, wildlife) and (2) dietborne exposure leading to direct effects on exposed organisms. For the former, the primary challenges are to predict the aggregate uptake of metal from both waterborne and dietborne exposure and to express that accumulation in terms that are appropriate to assessing risk to the consuming organisms. Issues that come into play in this scenario include whether forms of metal that are sequestered and detoxified by the aquatic organism are bioavailable to organisms that then consume those aquatic organisms. The available data to date suggest that metals can be sequestered/detoxified via different mechanisms/forms in an organism, with metals sequestered as inorganic granules having greatly reduced to no bioavailability to consumer organisms, while metals detoxified via metallothioneins have relatively higher bioavailability to consumer organisms (Wallace et al., 2003; Wallace et al., 1998; Mason and Jenkins, 1995; Nott and Nicolaidu, 1994). However, owing to different digestive physiologies and other factors, changes in the bioavailability of metals sequestered/detoxified by these different mechanisms or forms may occur (Wang, 2002). With respect to the second scenario, the literature is mixed on the degree to which this is an important pathway for inducing toxicity to aquatic organisms and how best to quantify exposure in that context.

4.4.2.2.1. ***Application.*** There currently are no standard approaches to assess dietborne exposures of metals to aquatic organisms in water quality assessments (Schlekat et al., 2001). For the organometallic compounds of organo-selenium and methyl mercury, dietborne exposure has been clearly shown to be a primary route of both uptake and toxic effects and should be considered in assessments of these metal compounds. Beyond those two compounds, the picture is much less clear. Toxicity to aquatic organisms from dietborne exposure to metals has been demonstrated where exposure is sufficiently high, although in some cases these concentrations are extreme (e.g., 10,000 µg/g Cu) (Handy et al., 1993). If the dietborne exposure necessary to elicit effects is exceptionally high, it is not clear that this pathway will drive ecological risk, as the environmental concentrations necessary to produce these exposures may be so extreme that ecological risk will occur via other pathways (e.g., direct toxicity of waterborne metal).

In other studies, however, effects from dietborne exposure have been demonstrated at relatively low exposure concentrations, such as in zooplankton studies (Hook and Fisher, 2002; 2001a, b). This raises much greater concern for metals assessment because it raises the potential for toxicologically significant exposures occurring in cases where risk via a waterborne pathway is low. That potential notwithstanding, other studies evaluating dietborne exposure with the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

same organisms and metals but somewhat different methods have reached different conclusions regarding the significance of dietborne exposure (De Schamphelaere and Janssen, 2004; Metzler, 2003). Dietborne exposure to metals is an area of active research, and it is likely that new insights will be forthcoming to rationalize what now appear to be conflicting data into a more comprehensive understanding of dietborne metal effects. Until that time, the absence of a standard approach will require that decisions regarding the handling of dietborne metal exposure in aquatic assessments be made on a case-by-case basis. Some bioaccumulation models for metals include consideration of dietborne exposure, although few, if any, link this accumulation directly to effects.

In the context of screening for exposure and potential risks to consumers, the use of whole-body inorganic metal concentrations in prey species may have some utility despite the uncertainties associated with trophic transfer and bioavailability of dietary metals (i.e., in cases where whole-body residues are below dietary toxic thresholds). For more definitive assessments, further research is needed on quantifying the bioavailabilty and effects of inorganic dietary metals (with the exception of certain organometallics where dietary toxicity has been well established).

In cases where trophic relationships are not well understood, stable isotope techniques can aid in defining the trophic status of species of concern and can be used to delineate the food web (i.e., who is feeding on whom). The ^{15}N concentration increases relative to ^{14}N concentration with each trophic exchange, and statistical models can link trophic status to metal concentration (e.g., Cabana et al., 1994). Additionally the potential for using stable (and radio)-isotopes of a metals can serve as a tools to understand dietary versus waterborne uptake, particularly in laboratory studies. Other uncertainties include how behavioral changes induced by dietborne metal exposure may affect the survival of the exposed organism (Irving et al., 2003).

4.4.2.2.2. ***Limitations.*** As indicated above, the primary limitation in assessing dietborne metal exposure for aquatic organisms is the absence of a broad understanding of the mechanisms underlying dietborne metal toxicity and the consequent lack of a standard assessment approach. Establishing rigorous residue/effect relationships that integrate waterborne and dietborne metal exposure is a critical consideration. When assessing dietborne exposure through direct measurement from field samples, there are methodological issues to be resolved, such as whether to depurate the digestive system of prey organisms. Metal contained in food or sediment within

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the digestive system will increase measured body burdens, but it may not have the same biological availability as metal residing within organismal tissues (Chapman et al., 2003). Fractionating body burdens of metals (e.g., cytosolic metal vs. metal granules) has been suggested as a better means of identifying the most readily accumulated fraction of dietborne metal (Seebaugh and Wallace, 2004; Wallace et al., 2003; Fisher and Reinfelder, 1995; Reinfelder and Fisher, 1994), although the interpretation of this information in the context of risk assessment has not been rigorously developed.

4.4.2.3. *Sediment Exposure*

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

Sediment Exposure Estimates

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

The most widely used approach for assessing metal exposure in sediment is based on EqP theory, with sulfides as the primary partitioning phase (Di Toro et al., 1990; 1991). Other approaches include sequential extractions with different media (water, weak acids, strong acids) or normalization to total iron or organic carbon. Each has its strengths and limitations. Detailed discussions are provided in Paquin et al. (2003) and Newman et al. (2004); additional information is provided in Section 4.5.9.

4.4.2.3.1. *Application.* Several approaches have been taken for estimating exposures to sediment-associated metals that account for bioavailability differences among various sediments. The EqP approach assumes that 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 metal should be present as sulfides and therefore relatively nontoxic. The amount of reactive sulfide is quantified

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

by measuring the amount of sulfide liberated when sediment is extracted with 1 N HCl. This procedurally defined quantity is known as acid-volatile sulfide or (AVS). The amount of reactive metal is determined from the same extraction by measuring the metal concentration in the acid extractant. This quantity is known as simultaneously-extracted metal or SEM. The potential bioavailability of metal is determined by comparing the relative molar concentrations of the two. 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 Class B or borderline Class B metals (Berry et al., 1996; Hansen et al., 1996; Ankley et al., 1996; Ankley et al., 1991; Carlson et al., 1991; Di Toro et al., 1990). See Section 4.5.9 for further discussion.

Although the correspondence of SEM-AVS to toxicity was found to be strong in these studies, some question 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). 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, the SEM-AVS model can be used in exposure estimations as long as its shortcomings are acknowledged appropriately.

Sem-AVS

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

Other tools for determining the exposure concentration of sediment-bound metals include metal concentrations in chemical (Fan and Wang, 2001; Babukutty and Chacko, 1995; Tessier et al., 1984), acid (Langston, 1980; Luoma and Bryan, 1978), or biomimetic (Weston and Maruya, 2002; Mayer et al., 2001; Chen and Mayer, 1998) extracts. However, no consensus yet exists on their best use for different types of metals or metalloids. Several

Exposure Assessments for Benthic Organisms

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

other methods have been proposed. Based on the premise that iron oxides in oxic sediments lower metal bioavailability, iron in a 1 N HCl sediment extract has been used to normalize metal exposure concentrations (Luoma and Bryan, 1978). Increasing concentrations of organic carbon can decrease metal bioavailability (Crecelus et al., 1982), so normalization of sediment metal concentrations to organic carbon content has been useful in other cases. The more readily extracted metals from sequential chemical extraction schemes tend to be the most bioavailable (Young and Harvey, 1991; Tessier et al., 1984) and can be used as exposure metal concentrations.

4.4.2.3.2. ***Limitations.*** Exposure assessment for benthic receptors could be enhanced if a clearer consensus were reached about the utility of each method for different classes of metals, biological species, and sediment types. Specifically, the following information is needed to improve exposure analysis: (1) improved computational or analytical methods for analyzing distribution of metal among components of the sediments, (2) improved computational methods for assessing the influences of metal form in sediments on sediment-water metal exchange, and (3) a better understanding of the processes controlling bioaccumulation of metals from solution and food by metazoan species directly exposed to the sediments (Luoma, 1989).

EPA (U.S. EPA, 2002f) published a report on the application of solid phase AVS equilibrium partitioning sediment benchmarks (ESBs) and interstitial water ESBs as No-Effect guidelines to predict sediments that are acceptable for the protection of benthic organisms. Details of the SEM-AVS method are discussed in Section 4.5.9 and the metals issue papers. The method has been applied to predict toxicity of metals in sediment for Class B or borderline Class B metals. An ESB based on the difference between the concentration of SEM and AVS is appropriate for protecting benthic organisms from the direct effects of sediment-associated metals, and not for estimating metal bioaccumulation. Chapman (2003) discusses limitations concerning the AVS-SEM approach, including the degree to which the EqP approach adequately represents exposures for organisms living in microenvironments in the sediment and/or who are exposed via ingestion of sediment. Site-specific measurements, where possible, are useful for confirming that generalized approaches like SEM-AVS appropriate for specific assessment scenarios. Furthermore, one should recognize that bioaccumulation of metal may still occur even when sulfides are in excess, and the potential consequences of this accumulation should be considered.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.4.2.4. *Terrestrial Species*

Terrestrial wildlife, plants, and invertebrates accumulate metals from direct contact with soil or sediment, from ingestion of contaminated food (plants or other animals), and from incidental soil or sediment ingestion. A conceptual model for direct and indirect exposure of terrestrial receptors to metals in soil is presented in Figure 4-6. Pathways of exposure include movement from soils through the food web, and to a lesser extent, air deposition either into soils or directly onto terrestrial receptors (e.g., plants). Because of significant differences in exposure patterns, it is more convenient to discuss methods by receptor group (invertebrates, plants, wildlife) rather than by pathways or environmental compartments.

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).

4.4.2.4.1. *Soil invertebrates.* The soil ecosystem includes a complex food web of soil invertebrates (both hard- and soft-bodied) that feed on each other, decaying plant material, and bacteria or fungi. For risk assessment purposes, however, exposure is described as a function of soil concentration rather than a detailed analysis of movement of metals through the food web. This is a reasonable approximation for soft-bodied invertebrates (e.g., earthworms) whose exposure is primarily through soil pore water (from both dermal absorption and soil ingestion) (Allen, 2002). There is more uncertainty in correlating soil concentrations with effects in hard-bodied invertebrates because they are primarily exposed through ingestion of food and incidental amounts of soil. (Sample and Arenal, 2001). Regardless, for all types of soil invertebrates, exposure estimates should account for differences in bioavailability among soil types, which include differential partitioning to soil particles and pore water, metal speciation, and aging. Each of these processes is discussed in detail in Section 4.1, Environmental Chemistry.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

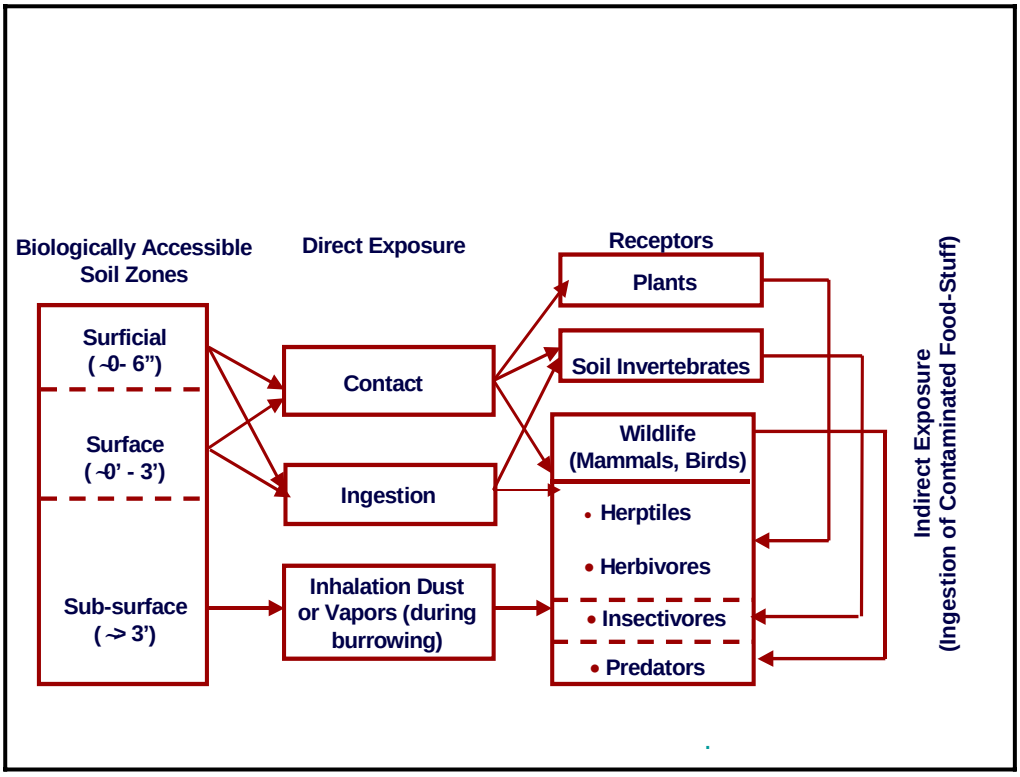

Figure 4-6. Conceptual model for direct and indirect exposure of ecological receptors to metals in soil zones.

Source: Menzie and Little (2000).

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

Cation exchange capacity (CEC) recently has been shown to be an important factor modifying zinc bioavailability in soils for both invertebrates and plants, 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 and oxyhydroxides present in the soil and is strongly pH

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

dependent. Surface charge on organic material and oxyhydroxides increases with increasing pH, thereby increasing their sorptive capacity for metals (thus decreasing metal bioavailability). Conversely, positive surface charges increase as the pH drops, increasing sorption of anions (e.g., arsenic or selenium) 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 to note that most published values of CEC are measured at pH 7.

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 (see Section 4.1.6.3 for a discussion of aging in soils). Preliminary studies suggest that consideration of aging may result in estimates of the bioavailable fraction as low as 0.1 × bulk soil concentrations. 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. Appropriate adjustments should be included in toxicity test protocols to simulate aging (McLaughlin et al., 2002), except when assessing acute (short-term) risks of spills.

4.4.2.4.1.2. ***Limitations.*** Data on CEC for field soils are often available, but similar information from laboratory studies of the toxicity of metal-spiked soil currently in not. Furthermore, the dependency of CEC on soil type (amount and type of organic matter, type of clay, and pH) also complicates the comparison among studies. Therefore, although exposure concentrations can be adjusted across field locations of similar soil type and pH, it is more difficult to make appropriate comparisons of field exposures with laboratory-generated concentration-response functions. Expressing exposure on the basis of pore water concentration is the goal, to reduce the variability in toxicity among sites; however, there are currently significant limitations to collecting and interpreting metal-related data from soil pore waters. Such information is not available in the published literature and, therefore, should be estimated using EqP theory (as with sediment pore water analyses). Published soil binding coefficients (K_ds) can be used, although these values are inherently uncertain as well (published value depends on derivation method, soil type, etc.; see Section 4.1.4 for a discussion on the limitations of K_ds).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.4.2.4.2. *Plants.* Plants access metals through the pore water, although mycorrhyzae, 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).

Metal Accumulation in Plants

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

4.4.2.4.2.1. *Application.* All plant species take up metals from soil through their roots via various mechanisms (Raskin et al., 1994; Cataldo and Wildung, 1978). The default approach to estimating exposure of plants to metal is measuring metal concentrations in bulk soil. However, as with soil invertebrates, this overestimates exposure because it does not account for differential bioavailability that results from complexation. Furthermore, with time, the bioavailability of soil metals may change due to dissolution or complexation; thus, "point-in-time" measurements of a soil may not reflect the future bioavailability. For example, Pb sulfide spilled onto soil (relative bioavailability 1–5%) with time would weather to Pb sulfate (relative bioavailability 50%), which could further evolve to sorb onto Fe oxides or phosphates (relative bioavailability 10–15, 30–59%, respectively). Soil pH, organic matter, and cation exchange capacity are the most important variables influencing bioavailability (see Section 4.5, Characterization of Ecological Effects). However, CEC and clay content are not consistently reported in the literature and therefore cannot be used to define relative bioaccessability and toxicity of metals. General categories of uptake based on soil pH and organic matter are shown in Tables 4-17 and 4-18 in Section 4.5 for ranges typically found in soils. These tables are a useful qualitative guide to identify soils with increased (or decreased) metal bioavailability. 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).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

4.4.2.4.3. *Wildlife.* The relative importance of exposure pathways and routes varies by species of animal as well as by metal, although, in general, wildlife exposure is primarily through diet and incidental ingestion of soils or sediments. The EPA has concluded that there are certain chemicals and exposure situations for which inhalation or dermal pathways are important, but under most situations they can safely be considered to be insignificant contributors to total metal loads (U.S. EPA, 2003c).

Exposure Pathway for Terrestrial Wildlife

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

bioavailability factors that are important in wildlife exposure, see Section 3.4.6.3, Ecological Effects (Wildlife).

4.4.2.4.3.1. *Application.* In the absence of site-specific information, the following generalizations can be used:

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

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

The relative importance of exposure pathways (soil vs. food chain) is dictated by the fraction of metal-contaminated soil in the diet and the amount of accumulation of metal in food items. Figure 4-7 provides a simple scheme for judging the relative contribution of food and soil before accounting for bioavailability. 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%.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Both the bioaccumulation factor and life history components interact to control the relative importance of soil or food as the primary metal transfer medium. In general, the following statements can be made about dietary uptake of metals from soil versus from food:

- If bioaccumulation is low (<<1), importance of soil ingestion versus diet for metal exposure increases.
- When bioaccumulation is greater (~1 or higher), the food pathway should dominate.
- 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.
- The looser the association with the ground (e.g., piscivores, aerial/arboreal insectivores, raptors), the lower the importance of soil ingestion.

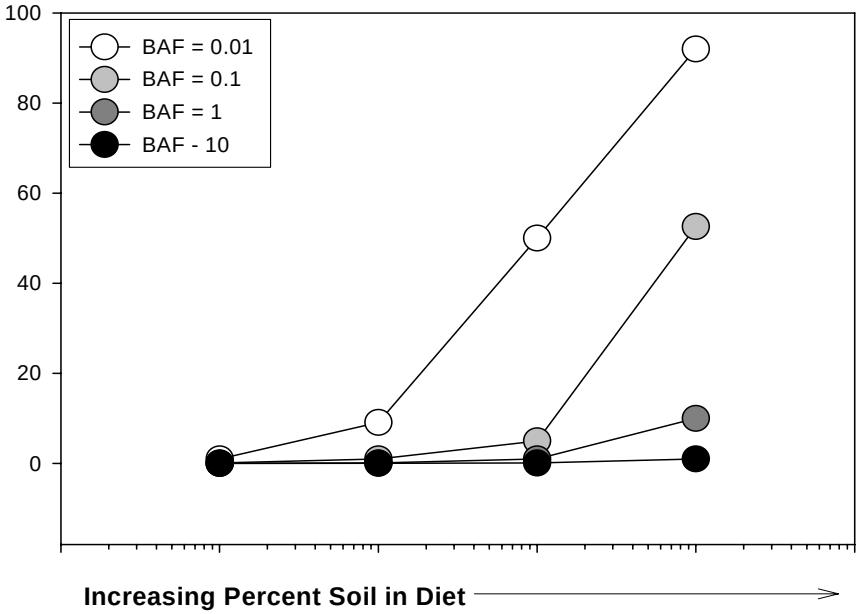

Figure - Generalized representation of percent contribution of incidental soil ingestion to oral dose for wildlife at different soil ingestion rates and bioaccumulation factors and a bioavailability of 100 percent.

Figure 4-7. Relative contribution of incidental soil ingestion to oral dose for wildlife at different soil ingestion rates and bioaccumulation factors, and a bioavailability of 100%.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Extrapolation from models developed for estimation of bioavailability of metals in soils for incidental human exposures may not be broadly applicable to all wildlife species owing to the influence of differences in digestive physiology and anatomy across the broad and diverse range of mammalian and avian species (Menzie-Cura and TN&A, 2000). For example, metals present in soils may be more or less bioavailable within the gut of an herbivore that relies on fermentation as compared to the simpler gut of a carnivore that is designed to break down proteins. These gut systems differ in chemistry (including pH) and residence time. For example, ruminants such as deer, antelope, and other hoofed stock initially process food through microbial digestion in the rumen, and their gut pH is general neutral or slightly acidic. Furthermore, end products of microbial digestion in domestic sheep bind to copper and enhance its uptake in the proximal intestine, resulting in a very low tolerance of these animals to dietary copper (NAS/NRC, 1980). Hind gut fermentors such as horses, rabbits, and granivorous birds (e.g., grouse or pheasants) also rely on microbial processes for digestion of lignen and other plant parts but have a more acidic foregut than do ruminants. Most insectivores and carnivores, on the other hand, have relatively acidic digestive systems with a significant amount of protein present. While the low pH may alter the metal speciation (or dissociate ions from attached ligands), most metals require active transport to move through the gut wall and into the circulation. This may be accomplished through binding with transporter proteins present either in the diet or within gastrointestinel cells, which likely differ among the wildlife species (Hill, 1979). Taken together, these physiological differences are significant and make it difficult to accurately extrapolate dietary toxicity thresholds across species. However, thoughtful application of this information will allow appropriate inferences to be made across species with similar physiology and may explain instances where statistical projections of toxic thresholds (e.g., species sensitivity distributions) appear to not be predictive of actual effects.

4.4.3. Food Chain Modeling for Wildlife

4.4.3.1. *Application*

Food chain modeling can be used to estimate the exposure of wildlife to metals based on ingestion of soil, food, and water. The basic format of the model is the same as that for organic substances and is shown in Figure 4-8; detailed explanations are available in several related documents (e.g., U.S. EPA, 2003c [EcoSSLs]; U.S. EPA, 1997d [ECOFRAM]; Sample et al., 1997). Measured, or predicted/estimated, concentrations of metals in soil, surface water, and

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

food items can be used in the model, or concentrations in food can be modeled using trophic transfer factors. TRIM.FaTE (http://www.epa.gov/ttn/fera/human_apex.html can be used for modeling media concentrations of metals as a result of aerial deposition. Information on diet, foraging area, and the like can be found in CH2M HILL (2001) and Sample et al. (1997). The absorbed fraction variable accounts for differences in relative bioavailability (RBA), and is either 1 (default value) or an appropriate estimate. Note that there is no relative absorption factor (RAF) included for food, because the default assumption is that site bioavailability equals that from the toxic form used in the toxicity tests

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

Trophic Transfer Values

Trophic transfer values for metals in terrestrial systems are an inverse function of soil concentrations; therefore, it is inappropriate to use constants for this term.

Sample et al. (1998a) developed uptake models to predict concentrations in earthworms from soil concentrations. These models can be used to estimate the exposure of both the worms themselves and of vermivorous wildlife (e.g., song birds, voles, and shrews). For selected metals (arsenic, cadmium, copper, mercury, manganese, lead, and zinc), the best estimate of tissue concentration in earthworms is a simple ln-ln regression. The addition of soil pH data to the regression model did not markedly improve fit. If soil calcium concentration was incorporated into the regression model, a better fit could be obtained for cadmium and lead but not for other metals. Tissue concentrations were inaccurately estimated for the transition metals nickel and chromium by both simple and multiple regression models. For general estimates, log-linear regression models may be used as bioaccumulation models for arsenic, cadmium, copper, mercury, manganese, lead, and zinc in earthworms. For site-specific assessments, it is recommended that location-relevant bioaccumulation models be developed through direct measurements of local soil and tissue concentrations.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Oral intake (mg/kg/day) =

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

where

$Soil_j$ =	Concentration for contaminant (j) in soil (mg/kg dw)
P_s =	Soil ingestion rate (proportion of FIR)
FIR =	Food ingestion rate (kg/kg-body weight/day, dw)
AF =	Absorbed fraction of contaminant (j) in biota type (i)
N =	Number of different types of biota in the diet
B_i =	Contaminant concentration in biota type (i) (mg/kg dw)
	Note: ($Soil_j \times T_{ij}$) can be substituted for B_i where T_{ij} = soil-to-biota trophic transfer factor (TTF) [as dry weight to dry weight] for contaminant (j) and biota type (I)
P_i =	Proportion of biota type (i) in diet (unitless)
AUF =	Area use factor; proportion of available habitat for a wildlife species within the area of concern (%)
$Water_j$ =	Concentration for contaminant (j) in water (mg/L)
WIR =	Water ingestion rate (mL/kg/day)

Figure 4-8. Wildlife Oral Exposure Model.
Source: U.S. EPA (2003c).

There is no compilation of plant biota/sediment accumulation factors (BSAFs), but U.S. EPA (2003c) (EcoSSLs) provides some data on select metals. For national-level assessments, uptake factors for plants provided by Efroymson et al. (2001) should be used. The highest accumulation of metals in plants occurs in the roots, although other parts of the plant also accumulate metals to varying degrees (Mitrofanov,1993; Greszta, 1982). With the exception of a few hyperaccumulator species, most plant species do not bioconcentrate metals (i.e., BAFs <1). Lead, arsenic, chromium, and cobalt are not taken up by plants in measurable quantities, and the small amount that is taken up is mostly confined to root tissues (Chaney et al., 2000; McGrath, 1995; Chaney and Ryan, 1994; Xu and Thornton, 1985). Exceptions to this exist, notably including, but not limited to, Se and Mo: uptake of these metals into the edible portion of plant

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

tissues can be quite high, generally not sufficient to cause plant toxicities (McGrath, 1995; Bingham et al., 1986; Foy et al., 1978), but may cause significant food chain toxicities .

In contrast, plants are quite sensitive to some metals (manganese, zinc, copper, for example) and may die before achieving high levels that pose a threat to animals via food chain transfer.

4.4.3.2. *Limitations*

Food chain modeling for wildife is similar for both metals and organic substances. All estimates are limited by the information available about the receptor(s) of concern in terms of dietary preferences, relative amounts consumed of various items, relative bioavailability between laboratory and field, and other factors (see Figure 4-8). For metals, the largest uncertainty in the dietary uptake model is in the estimates of trophic transfer factors. As discussed above, these generally are not constants and therefore require the use of uptake equations (i.e., tissue concentrations vary as a function of soil concentration). This necessitates the use of at least quasi-probabilistic modeling, rather than a more simple determination of a single, deterministic oral uptake value.

Use of either measured or modeled tissue metal accumulation levels as an indicator of potential toxicity is limited by the requirement that the accumulated amount be related to a benchmark effect level (i.e., Critical Body Residue, CBR). Very little information is available for metal CBRs in terrestrial wildlife. This is particularly problematic when whole-body tissue levels are reported because what really matters is the effective metal concentration at the site of action of toxicity. If the concentration at the proximate site of action of toxicity is proportional to the whole-body concentration, then this is a lesser concern. However, if the concentration at the site of action is not proportional to the whole-body concentrations, then direct measures of metal concentrations at the site of action is required, especially at higher assessment levels.

Furthermore, the absolute level of metal accumulation is not as important as the rate of uptake (Hook and Fisher, 2002; Hook, 2001; Roesijadi, 1992). High uptake rates overwhelm the ability of organisms to sequester or excrete the metal, leaving larger proportions of the accumulated metal in a more bioavailable form. Uptake is believed to occur because of the ability of some organisms to sequester metals that enter the cell (e.g., by inducing the synthesis of metallothionein [MT] or granule formation). Adverse effects are avoided as long as the rate

If the concentration at the site of action is not proportional to the whole-body concentration, then direct measures of metal concentrations at the site of action is required, especially when conducting detailed, higher level assessments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of metal uptake does not exceed the rate at which the organism is able to bind the metal, thereby preventing unacceptable increases in cytosolic levels of bioreactive forms of the metal. If the rate of uptake is too great, the complexation capacity of the binding ligand (e.g., MT) could be exceeded; cytosolic metal levels then become unacceptably high, and adverse effects could ensue. Because measures of uptake rates are not available, static concentrations are used instead.

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

In sum, the following factors contribute significantly to uncertainty in food chain models:

- Soil ingestion rates are highly uncertain.
- Diet composition can be highly variable, and diet composition has a significant effect on exposure.
- Relative bioavailability from foods is completely unknown.
- Modeling over a number of trophic levels propagates uncertainty.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5. CHARACTERIZATION OF ECOLOGICAL EFFECTS

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

4.5.1. Essentiality

Essentiality

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

Essentiality, or the requirement for normal organism metabolic function, of many metals is one of the primary factors that differentiates risk assessment for metals and metal compounds from that of synthetic organic chemicals (Janssen and Muyssen, 2001). Some trace elements, such as cobalt, copper, iron, manganese, selenium, molybdenum, and zinc, are necessary for the normal development of plants and animals. In many cases, these metals are added to animal feed and pharmaceutical products (SRWG, 2002) or to plant fertilizers. Other metals, such as arsenic, cadmium, lead, and mercury, are not known to be essential to plant and animal growth and development. Trace elements can be divided into three groups:

- Those known to be essential.
- Those that have beneficial metabolic effects but have not been shown to be essential.
- Those that occur widely in living organisms but seem to be only incidental contaminants and are not known to be beneficial (Mertz, 1981).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-14 classifies the metals addressed in this framework by their known essentiality to organisms. The concept that many metals are required for organism health at one range of concentrations and are toxic in quantities outside of that range has been referred to as the "window of essentiality" (Hopkin, 1989) or the "optimal concentration range" for essential elements (Alloway, 1995; Fairbrother and Kapustka, 1997; Van Assche et al., 1997). For essential elements that exhibit biphasic dose-response curves (Figure 4-8, above), adverse effects resulting from deficiency should be considered, as well as those that result from excessive exposure. Recognition of the window of essentiality, as well as consideration of the biochemical and physiological processes that regulate metals within living organisms, are both important components of ecological effects assessment (Abernathy et al., 1993).

4.5.1.1. Application

The optimal concentration range (or safe intake range) for essential elements should ensure that effects thresholds such as Toxicity Reference Values (TRVs) are not lower than the nutritional requirements for the particular plant or animal species being evaluated. Where TRVs or other effects concentrations (or doses) are intended as thresholds for detrimental effects due to excessive intake), care should be taken to ensure that these toxicity thresholds for essential metals are at the upper end of the optimum range or sufficiency range (at the point where toxic effects begin to occur). If set too low (i.e., in the range where deficiency can occur), the determination of risk will be erroneous. For wildlife, the literature on dietary requirements of essential elements for livestock can be consulted. The NAS/NRC has published useful summaries (NAS/NRC, 1994, 1980), and McDowell (2003) updates this information. Minimum concentrations required for plant growth are summarized in Marschner (1995).

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, to directly compare toxicity threshold values with recommended dietary requirements because of differences in test conditions among published studies.

In screening-level assessments, toxicity threshold values are advised for application, if they are 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.

4.5.1.2. Limitations

Because of differences in test conditions among published studies, it may be difficult to directly compare toxicity threshold values with recommended dietary requirements of essential elements. Extrapolation of data among species (e.g., from livestock to wildlife species) also may

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

add uncertainty to the effects assessment. Furthermore, addition of safety factors when deriving protective values often results in concentrations significantly below required intake. Derived toxicity threshold values should be used in screening-level risk assessments if they are not lower than estimated requirements. Uncertainty in toxicity thresholds or estimated requirements should be addressed as part of the risk management process. Higher level assessments, where more accurate estimates of effects thresholds are expected, may require additional bioassays to characterize the biphasic dose-response curve and determination of both required and excessive threshold levels. See the following sections for considerations of bioavailability factors, mixtures of multiple metals, and interspecific extrapolations.

Table 4-14. 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	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.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.2. Acclimation and Adaptation

Organisms have developed various mechanisms to cope with variable background metal concentrations, particularly for those metals that are essential elements (see Table 4-14). If the amount is less than required, passive or active uptake mechanisms are used to enhance internal concentrations, whereas during periods of excessive amounts exclusion mechanisms come into play. These various approaches to homeostasis are discussed in detail in Kapustka et al. (2004). Additionally, organisms can acclimate to suboptimal metal levels by changing various physiological functions, or populations can undergo genetic adaptation and develop increased tolerance to different levels (Rusk et al., 2004; Wallace and Srb, 1961).

The genetic makeup of an organism defines its ability to cope with environmental conditions. Genes can be expressed or remain "silent," and shifts in gene expression can occur when the environment changes. Furthermore, organisms use different portions of their total array of genetic information in different life stages. This shifting of tolerance within the genetically defined limit of the organism is known as *acclimation*. Physiological changes induced by acclimation may be reversed if the environment reverts to the original conditions (Posthuma and Van Straalen, 1993; Prosser, 1986). Tolerance acquired through physiological acclimation processes is not always passed on to offspring; however, the same genetic information that allowed acclimation to occur in the parents will be passed on, so the offspring will retain the ability to acclimate in a similar fashion. If the offspring develop in the altered environment, they will express the set of genes most appropriate for tolerance of those conditions.

Tolerance, Acclimation, and Adaption

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

Costs of Metal Tolerance

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

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.2.1. *Application*

Metal tolerances of plants and livestock are summarized in Table 4-15. It should be noted that the NAS/NRC (1980) committee that identified the maximum levels of metals tolerated by domestic livestock based its conclusions on data from toxicological-type feeding studies in which soluble metal salts had been mixed with practical or purified diets to examine animal response to the dietary metals. If soil is incorporated into diets, metal solubility and bioavailability may be much more limited than in the tests relied on by the NRC. For example, it has been noted that until soil exceeds about 300 mg Pb kg^{-1}, animals show no increased body burden from ingesting the soil (Chaney and Ryan, 1993). Other metals in equilibrium with poorly soluble minerals or strongly adsorbed in soils are often much less bioavailable than they would be if they occurred in more soluble salts.

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

PICT

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-15. Maximum tolerable levels of dietary minerals for domestic livestock compared with levels in forages

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

[a]Indicates whether a plant will die at concentrations lower those that which will affect animals.
[b]Based on literature summarized in Chaney et al. (1983).
[C]Based on NAS/NRC (1980). Continuous long-term feeding of minerals at the maximum tolerable levels may cause adverse effects. NRC estimates levels by extrapolating between animal species when data are not available.
[d]NRC based the maximum levels tolerated of Cd or Pb in liver, kidney, and bone in foods for humans rather than simple tolerance by the animals. Because of the simultaneous presence of Zn, Cd in animal tissues is less bioavailable than Cd salts added to diets.
Yes = Plant dies; Fails = Plant does not act as a barrier and concentrates metal to levels for toxic animals;
? = Unknown.

Most research examining tolerance to metals has focused on population-level responses, although consequences at the community level also occur. The most common explanations for increased tolerance of populations within communities include acclimation and selection for resistant genotypes. However, because communities consist of large numbers of interacting species, it is likely that other mechanisms unique to these systems will contribute to increased

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

tolerance. For example, the replacement of sensitive species by tolerant species, termed "interspecific selection" (Blanck et al., 1988), is a common response in polluted systems and one of the most consistent indicators of metal pollution. Pollution-induced community tolerance (PICT) has been proposed as an ecotoxicological tool to assess effects of contaminants on communities (Blanck et al., 1988). PICT is tested by comparing responses of communities collected from polluted and reference sites to contaminant exposures under controlled conditions. The increase in community tolerance at a polluted site that results from the elimination of sensitive species is considered evidence that this restructuring was caused by the pollutant.

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

For assessments conducted for regional or national assessments, criteria development, or ranking purposes, it should be acknowledged that results will be based on organisms and soil types that result in greatest bioavailability and sensitivity. Care should be taken, however, that the organism-environment combinations that are assessed are, in fact, compatible with real-world conditions. For example, benthic organisms generally associated with slow-moving, warm waters would not be expected to tolerate conditions of high metal biovailability such as those occur that in faster-moving, colder waters that have little organic matter. Thus, for site-specific assessments, species tested and water (or sediment) used in the test system should be similar to conditions at the site. In the absence of such information, data from standard test species and conditions could be used, but uncertainty factors may be warranted to adjust the final toxicity value accordingly.

More appropriately, single-result assessments for the entire country should be avoided. Rather, such assessments should be subdivided into metal-related ecoregions known as "metalloregions" (McLaughlin and Smolders 2001) so that protection levels, mitigation goals, and ranking results will be appropriate for the suite of species naturally present within each type of controlling environment. This is directly analogous to the use of ecoregions when

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

establishing WQC (Griffith et al., 1999). The value of metalloregions is that they provide the conceptual framework to account not only for the broad regional parameters affecting metal availability in soils and waters, but also for the differences in organism response to added metal.

4.5.2.2. *Limitations*

Although there is considerable evidence to support the hypothesis that previously exposed populations will be tolerant to metals, both physiological acclimation and adaptation to contaminants may have specific costs (Wilson, 1988). For example, although induction of metal-binding proteins increases tolerance to subsequent metal exposure, it also uses energy normally available for other metabolic processes (e.g., growth, reproduction). Similarly, genetic changes associated with exposure to contaminants might harm populations. Reduced genetic diversity has been reported in populations exposed to contaminants and may result in population bottlenecks. Furthermore, as tolerant genotypes are eliminated from a population, the reduced genetic diversity may increase the susceptibility of this population to other stressors. There is theoretical support for the hypothesis that populations adapted to contaminants have higher metabolic costs or are more susceptible to other stressors (Hoffman and Parsons, 1997; Mulvey and Diamond, 1991); however, few empirical studies have demonstrated increased costs.

Metalloregions

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

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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 OM) should be overlayed on the ecoregions, along with soil type (e.g., sandy loam, clay loam) and background metal concentratons of metals. Similar information is needed for water bodies. Although this type of information is fairly current and available, soil data have not been updated since the mid-1970s, which may limit their usefulness to some extent. Nevertheless, work is under way to develop metalloregions, although it is likely to be several years from the time of this writing before they are available for use in a decision-making capacity.

4.5.3. Metals Mixtures

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

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

Much of the difficulty in interpreting the available information on the toxic effects of metal mixtures is due to differing measures and definitions of the bioavailable fraction of metals, whether it is the fraction that is available for uptake from the environment or at the site of toxic action. Some measure of the bioavailable metal fraction in the exposure media is needed to accurately predict the effects of metals and metal mixtures (Di Toro et al., 2001; Sauvé et al., 1998; Weltje, 1998; Posthuma et al., 1997; Ankley et al., 1996). Characterization of effects of metal mixtures has also been reported to be concentration dependent (Mowat and Bundy, 2002; Fargašová, 2001; Herkovits et al., 1999; Spehar and Fiandt, 1986).

4.5.3.1. *Studies of Metal Mixtures*

Few controlled studies exist on the toxicologic interactions of metals found in environmental contamination scenarios. ATSDR has compiled and evaluated interaction studies involving various metals: methyl mercury, arsenic, cadmium, chromium, lead manganese, zinc, copper, cesium, cobalt, strontium, and uranium (draft interaction profiles available online at

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

http://www.atsdr.cdc.gov/iphome.html). Few studies allowed any quantification of interaction magnitude, whether using the authors' definitions of toxicologic interaction or EPA's definitions based on dose and response addition. The summaries below indicate some of the qualitative conclusions available on interaction potential.

A study of a mixture of cadmium, lead, and zinc in rats found slightly more marked adverse hematological effects with the ternary mixture exposure than with the cadmium-lead, cadmium-zinc, or lead-zinc mixtures (Thawley et al., 1977); inconsistencies in dietary levels of calcium and vitamin D in this study, however, may have made comparisons problematic. A well-controlled rat study has reported significant synergism between cadmium and lead regarding testicular atrophy (Saxena et al., 1989). That study also demonstrated protective effects of high dietary levels of zinc, which effectively reduced the testicular effects of the cadmium-lead mixture to control levels. No studies have been located that would allow extrapolation of those high exposure results to more common, lower environmental levels. In another study (Fowler and Mahaffey, 1978), a relatively wide range of endpoints were investigated in studies that covered each metal singly and all possible binary and ternary mixtures. Body weight gain was depressed equally by the ternary mixture and the cadmium-lead mixture, and to a lesser extent by the arsenic-lead and cadmium-lead mixtures, whereas food utilization was depressed more by the ternary and arsenic-cadmium mixtures than by the other binary mixtures. In general, the biological parameters studied in this report indicated changes of smaller magnitude and inconsistency in direction for binary mixtures compared with ternary mixtures.

The data regarding interactions of environmental metals usually are not adequate for predicting the magnitudes of interactions. Interaction profiles by ATSDR of metal-metal interactions have considered the following combinations: arsenic, cadmium, chromium and lead; lead, manganese, zinc, and copper; and cesium, cobalt, and strontium (see above Web site for draft reports). Experimental efforts to identify and quantify interaction mechanisms among these metals are needed. For some endpoints, the data are not robust enough to show even the direction of interaction (i.e., whether the joint action will be dose additive or greater than or less than additive). The animal studies discussed briefly in this report used commercial diets or semi-purified diets that may have higher or lower levels of essential metals than human diets. Much higher doses of the metals appear to be required to elicit effects when commercial diets are used than when semi-purified diets are used. At the other extreme, effects are seen at very low doses when deficient diets are used. Comparisons among studies are therefore problematic, particularly when the diets are not specified.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.3.2. *Mixtures*

Similar to human health risk assessments, ecological risk assessments commonly involve mixtures of metals. However, Agency guidance is less developed for how to estimate metal mixture effects for wildlife. Binary interactions of dietary metals in livestock are discussed in NAS/NRC (1994, 1980) and McDowell (2003). These references can be used as sources of information from which at least qualitative estimates of additivity, synergy, or antagonism can be developed. Additionally, see section 4.3.6.3. for discussion of human health assessment for mixtures, which provide information useful in consideration of wildlife effects.

4.5.3.3. *Application*

Two key questions should be addressed by effects assessments related to metal mixtures:

- To what extent does each metal contribute to any observed effect?
- Are the effects significantly greater than or lesser than the sum of the individual component effects?

The answers to these questions also have the potential to affect water quality guidelines (WQGs), EcoSSL values, cleanup targets, and other similar management decisions.

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

In the Concentration Addition model, all metals in a mixture are added together to predict toxicity; 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 convert all metals to one metal concentration). In the Effects Addition model, differing potencies are ignored, and the effect of each metal's concentration in a mixture is combined to predict mixture toxicity. Only the Concentration Addition model allows detection of toxicity greater than predicted (more than additive); the Effects Addition model can only predict strict additivity.

The TU approach involves deriving dimensionless units for each metal in a mixture by dividing individual concentrations by their individual toxic concentrations (such as LC_{50} values).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The TUs for all the metals in the test mixture are then summed. A value of 1 ± 0.1 in the case of an LC_{50} would predict 50% mortality (or another effect if TUs are based on that effect rather than on lethality). A value significantly greater than 1 would predict more than 50% mortality. A value significantly less than 1 would predict less than 50% mortality.

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

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

where TTM is the predicted total toxicity of the mixture, C_i is the concentration of the component, and WQG_i is the guideline for that component. If TTM exceeds 1, then the mixture has exceeded the water quality guideline. It is important to note that this has been developed for water, and significant limitations may be associated with applying it to soil systems.

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

Application of HSAB. The QICAR approach (described in Section 4.1, Environmental Chemistry) might also be applicable to predict the potential for interactions of metals in mixture. Unsatisfied with the qualitative conclusions of Newman and McCloskey (1996), Ownby and Newman (2003) fit binary metal mixture data derived from the Microtox assay to the following model of joint independent action (Finney, 1947):

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

where:

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

P_{A+B} = The biological response to the metal mixture, expressed as a proportion
P_A and P_B = The biological responses to A or B when present singly

This relationship would hold if the actions of the paired metals were independent. However, if the metals were not independent, the P_AP_B term will deviate from its expected value of zP_AP_B where z = 1. Assuming that paired metals with very similar binding tendencies are more likely to interact with the same biological ligands than are metals with very dissimilar tendencies, deviations of the z coefficient from 1 would reflect departure from complete independence of metal action. HSAB theory allowed prediction of metal interactions in this model system. Although Microtox is considered to be a useful tool for organic contaminants, it is very sensitive for metals (Willemson et al., 1995).

4.5.3.4. *Limitations*

At present, the most appropriate approach for determining the toxicity of metal mixtures and addressing the two key questions listed above is to use the TU approach as a screening-level assessment. This approach cannot, however, be used beyond screening because it does not provide enough certainty. Norwood et al. (2003) found that of 191 case studies examined, 70% were additive or less than additive. Thus, this approach was primarily either appropriate or overprotective, but 30% of the case studies indicated that this approach would be underprotective. For aquatic organisms acutely exposed to cationic metals, the assumption of additivity is sufficient, particularly if bioavailability adjustments are made using the BLM (see Section 3.4.8).

Toxic Unit Approach

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

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

Researchers are presently attempting to predict the effects of metal mixtures on the basis of critical body concentrations of metals. Ongoing research is attempting to integrate the effect

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

accumulation functions of each metal into a metal mixture model in which an effect addition formula will be compared with a concentration addition formula, both based on body concentration. Current work is focused on aquatic invertebrates, and similar research is required for other organisms.

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

4.5.4. Background

Background is defined as the amount of metals occurring in soils, water, or air as a result of anthropogenic and natural processes. Anthropogenic contributions are limited to those that are not influenced by current, direct releases (i.e., emissions, discharges, or disposal) from a source or site of concern. This includes metals that may arise from manmade substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that are not specifically related to the release in question (U.S. EPA, 2003c). Background should be defined in a specific spatial and temporal aspect that is related to the scope of the particular hazard or risk assessment. Background concentrations can vary by as much as five orders of magnitude, depending on soil type, geography, and other factors (Chapman and Wang, 2000).

Background

Background is defined as the amount of metals occurring in soils, water, or air as a result of anthropogenic and natural processes. Anthropogenic contributions are limited to those that are not influenced by current, direct releases (i.e., emissions, discharges, or disposal) from a source or site of concern. This includes metals that may arise from manmade substances (particularly metalloids) or from natural substances (metallic ores) present in the environment as a result of human activity that are not specifically related to the release in question. Background can exacerbate toxicological effects and accumulations from direct emissions or other sources, or conversely it may result in adaptation of organisms to higher metal concentrations and result in increased tolerance to emissions.

Background may exacerbate toxicological effects and accumulations of metals from direct emissions or other regulated sources or, conversely, it may result in adaptation of organisms to higher metal concentrations and result in increased tolerance to emissions (see

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

above section). Furthermore, because metals occur naturally, and some are essential macro- or micronutrients, they are at least partially responsible for how plants and animals are distributed within various ecoregions. The distribution of plants and animals, local species diversity, species survival, and the vitality of individuals can be profoundly affected by background levels of metals in an area. Humans, on the other hand, are distributed throughout the world, irrespective of naturally occurring levels of metals, so knowledge of background levels is not as significant.

4.5.4.1. *Application*

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

A more appropriate approach is to define average (and ranges) of background concentrations for various ecoregions (Hargrove and Hoffman, 1999; Bailey, 1998; Omernick, 1986). Work is under way in this regard, but such values currently are not available. Therefore, the recommended default is to use state averages where possible and always to define the range that might be encountered within the spatial scale being considered. It is also important to recognize that background concentrations in water are highly variable through time because flooding or drought conditions substantially change the relative concentrations of metals in a water body. Again, it is suggested that ranges rather than single number averages be used.

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

Another reason to include background in the assessment is to evaluate the effect of the remedial options. Although some areas of the site may have elevated concentrations for certain metals, other metals may not be elevated. Remedial actions could cause these naturally occurring metals to become more bioavailable, thereby resulting in unintended toxicity. The HSAB theories and QICAR models (see Section 4.1.2) can be applied to derive useful estimates of biological activity for metals to aid in making decisions regarding remedial actions.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the *bioavailable fraction* of the natural background concentrations should be added to the *bioavailable fraction* of the added metal.

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

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

4.5.4.2. *Limitations*

National databases of metal concentrations in soil or water do not currently differentiate between naturally occurring levels and levels that are elevated owing to anthropogenic sources. However, the databases can be screened to ascertain whether specific areas are affected by point source emissions and so can be used as reasonable estimates for large-scale background levels. More important, however, is that background concentrations are most frequently reported as total amount of metal, without specifying the bioavailable fraction or chemical speciation or the data (e.g., pH or redox potential) needed to estimate bioavailability. Information on probable mid- to long-term changes in soil or water properties that might enhance bioavailability of background metals also should be provided for accurate assessments of future risk.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.5. Indirect Effects of Metals

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

Indirect Effects

Indirect effects to organisms initiated by metals toxicity can be negative (density dependent or independent) or positive (density dependent) and can occur between species or within the same species. Table 4-16 summarizes some of these relationships.

Indirect effects to organisms initiated by metals toxicity can be negative (density dependent or independent) or positive (density dependent) and can occur between species or within the same species. Some examples are summarized in Table 4-16; additional examples are provided by Chapman et al. (2003). Interactive effects can also occur due to the combined effects of environmental stressors and metals toxicity. For instance, Liess et al. (2001) found that the toxicity of copper to an Antarctic amphipod was increased by food shortage and excessive ultraviolet-B radiation. Some authors have considered such interactive effects to be indirect; however, they can be addressed as direct effects in risk assessments and hence are not considered further.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-16. Examples of Indirect Effects of Metal Toxicity

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

4.5.5.1. *Application*

Functional redundancy (species having similar roles in ecosystem processes) is a well-known but arguably not well-understood phenomenon in ecosystems. It is often assumed that if an organism's primary prey item is reduced or eliminated, then the organism can switch to another prey item due to functional redundancy. However, in the case of food web-mediated effects, the following sequence can and does apply: chronic metal exposure reduces the food abundance of certain dietary components; as a result there are increased energetic costs of feeding and an associated reduced growth efficiency. It is important that all components of the food web are exposed to metals; thus, the determination of the final effect should include the concurrent changes to all elements.

A determination of whether indirect effects such as loss of preferred prey can occur requires three components. First, appropriate conceptual diagrams should be developed in the problem formulation phase of the risk assessment and subsequently refined. Such diagrams should incorporate sufficient detail regarding key biotic interactions (e.g., competition and predation) and the ecological context in which the species exist and pollution occurs. As noted by Chapman et al. (2003), seasonal and life-stage changes in feeding patterns can occur and will "require iterative temporal diagrams showing the various reasonable possibilities." If the factor is limiting, then the organism will exhibit a response; however, if it is not a limiting factor, the likelihood that it will lead to organismal changes decreases.

Second, risk assessors should focus proactively on the first three possibilities in Table 4-16 because it is extremely unlikely that indirect effects due to density-dependent compensation will be detectable without extraordinary effort. Increased numbers of receiver organisms due to reduced competition or predation are more likely to be detected and more likely to have overall

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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

Third, risk assessors should focus on any cases of reduced growth of individuals, particularly where the individuals affected are relatively tolerant to metals toxicity *and* their normal feeding patterns are disrupted. These are clear indications (although not conclusive proof) of indirect effects of metals toxicity. An example of negative indirect effects due to reduced prey is provided by Campbell et al. (2003). These authors summarize extensive field research into yellow perch in metal-impacted lakes in eastern Canada. Yellow perch in lakes shift from feeding on zooplankton to feeding on littoral macrobenthos during their second year of growth and then begin to include a significant amount of fish in their diet during their third to fifth year of growth. Fish in the most metal-impacted lakes did not undergo this normal sequence of diet shifts. Instead, they continued to utilize smaller prey throughout their lives owing to the loss of their primary prey species to direct metal toxicity. A bioenergetic bottleneck developed because the perch's growth efficiency was reduced by the need to catch and eat smaller prey. The perch were more tolerant to metals toxicity, and thus there were no major direct effects on their survival (though multiple physiological effects were recorded). However, the loss of their primary prey species resulted in smaller or stunted perch, a major indirect effect of metals toxicity. Many methods exist in the ecological literature to gather population, community, or ecosystem function data that may be achieved without significant levels of effort. Some elegant analyses of population demographics can be accomplished within a single sampling effort (e.g., Wilson et al., 1996; Heyer et al., 1994; Davis, 1982).

4.5.5.2. *Limitations*

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

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

Presently there is no realistic means of ranking metals on the basis of indirect effects, nor are national criteria possible. This remains a site-specific issue because interactions between the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

initiator (metal toxicity), the transmitter, and receptor organisms are dependent on both the level and type of toxicity and the sensitivities of individual organisms within structurally and functionally unique populations, communities, and food chains.

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

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

4.5.6. Bioavailability in Terrestrial Systems

Bioavailability of soil metals to terrestrial organisms is closely linked to dynamic soil physical and chemical parameters, and biotic processes. As discussed in Section 4.1, there are qualitative and quantitative methods and models for considering soil chemistry issues and aging of metals in soil that modify metal bioavailability and its toxicity in soil. Unless specific bioavailability data exist, even with measures of soil physical and chemical parameters such as soil loading capacity, aging of metals, and speciation, accurate estimates of exposure to the terrestrial biota cannot be made. In situations where information is not available, bulk soil chemistry is typically used with a default of 100% relative bioavailability.

Unless specific bioavailability data exist, even with measures of soil physical and chemical parameters such as soil loading capacity, aging of metals, and speciation, accurate estimates of exposure to terrestrial biota are not possible. In situations where information is unavailable, bulk soil chemistry is typically used with a default of 100% relative bioavailability (i.e., the bioavailability of the chemical in soil is presumed to be the same as the bioavailability in the tests used to develop the toxicity data).

4.5.6.1. *Soil Organisms: Invertebrates and Microorganisms*

Metal speciation is the primary consideration in assessing the bioavailability of metals to soil invertebrates and microbes. Major assumptions regarding metal exposure in aquatic systems, such as a the relatively homogeneus dissolution of metals in the exposure water, may not be applicable or may apply at different scales in soil systems. Although soil microbes may

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

be immersed in soil solution films surrounding soil particles, few invertebrates are exposed to metals in this manner. Exposure usually consists of partial contact of soil solution films with the surfaces of the invertebrates that are capable of absorbing metals (e.g., earthworm dermal surfaces). Direct contact with membranes across which metal uptake can occur does not take place for many hard-bodied soil invertebrates (e.g., arthropods), and metal uptake is almost entirely through the ingestion of metal associated with particle matter or soil solution. For these reasons, exposure and relative bioavailability cannot be expressed similarly for each organism in the soil ecosystem, and an understanding of primary routes and mechanisms of metal exposure should be established for species or groups of similar organisms.

Exposure and relative bioavailability cannot be expressed similarly for each organism in the soil ecosystem, and an understanding of primary routes and mechanisms of metal exposure should be established for species or groups of similar organisms.

Often, direct toxicity testing of the soil of concern is the best method for assessing bioavailability and toxicity-to-soil biota (Fairbrother et al., 2002). Issues such as spiking of metals solutions onto soils, aging, and laboratory-to-field extrapolation should be considered. In the ecological soil screening document (U.S. EPA, 2003c), published literature was evaluated using primary soil parameters affecting lability of metals in soils in a matrix to qualitatively indicate metal bioavailability. Further information on this topic and factors relating soil chemistry to soil biota toxicity are discussed in Section 4.1.6. A terrestrial BLM method currently under development (Allen, 2002) may provide a useful tool to link bioavailability, soil chemistry, and toxicity to soil biota.

4.5.6.2. *Plants*

Ionic or organometallic complexes that increase the total concentration of elements at the root surface have been correlated with increased uptake, either through disassociated ions or through uptake of intact complexes. Thus, research into how to quantify metal complexes in soils relative to their lability is important.

The most common route of metal exposure in plants is through the roots. Ions and organic molecules contact roots via the transpiration stream, diffusive transport, and microbe-facilitated transport. At the root surface, soluble contaminants have the potential to enter the root tissue through the transpiration stream or through a range of mechanisms designed to facilitate nutrient uptake. In general, it is thought that only uncomplexed, free ionic species of cations and ions can be taken up by roots. This has been described using a FIAM (Parker and Pedler, 1997; Lund, 1990). Sauvé et al. (1998) put forward

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

a method to calculate free metal activity levels for copper and lead to derive a pH-dependent soil criterion for soil biota. The soil criteria paper was based in part on previous studies (Sauvé et al., 1997a, b, 1995; McBride et al., 1997) to generate models to predict free copper activity from total metal content, pH, and organic matter content or, in the case of lead, using only total metal levels and pH. The equations were generated from more than 60 soils using ion selective electrodes and standard methods for determining pH, organic matter content, and total metal levels. However, many exceptions to the FIAM have been identified, such that it has been abandoned in favor of its close cousin, the BLM. Ionic or organometallic complexes that increase the total concentration of elements at the root surface have been correlated with increased uptake, either through disassociated ions or through uptake of intact complexes (Parker et al., 2001; McLaughlin et al., 1994). In addition, it is clear that plants do not distinguish well between many pairs of ions of similar charge and size (e.g., As and P or Cd and Zn).

Plant bioassays can be used to measure the relative bioavailability of metals in various soil types. Results can be used to determine either the direct or the indirect value of bioavailability of contaminants in plants and to extrapolate an indirect estimate of relative bioavailability to organisms that consume the plants (assuming a correlation between plant and animal uptake). This type of testing has been routinely done in agriculture for decades and has been used to validate extraction tests. Tests have most often focused on identifying plant deficiencies of particular elements, but they are easily adapted to evaluate toxicities (Gettier et al., 1985).

In the absence of test data, relative bioavailability can be estimated qualitatively based on relative pH and organic matter content (Tables 4-17 and 4-18), although other soil factors can be significant, most notably CEC. However, combinations of these two soil parameters and their ranges are sufficient as a qualitative guide for assessors to identify soils where metals may have increased (or decreased) availability to plants. This is particularly noted when soil pH exceeds 7 and is a mechanism to obtain essential elements under conditions of low availability.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Table 4-17. 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 4-18. 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 (2003e).

4.5.6.2.1. ***Critical Tissue Residues.*** When used appropriately, plant tissue analysis can provide an indirect, semiquantitative assessment of bioavailability processes (NAS/NRC, 2002). For phytotoxic metal concentrations to be effectively used as an indirect measure of bioavailability, it is important that the threshold values of the plant tested be well understood. In addition, toxicities of certain metal elements are associated with deficiencies of others. For example, increased zinc, copper, and nickel toxicities can be associated with iron deficiencies (Bingham et al., 1986), and increased lead and zinc toxicities can also be related to phosphorus deficiencies

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(Brown et al., 2000, 1999a; 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). Because of these multiple confounding factors, the bioavailability of metals in plants (as well as to consumers) is more accurately and reliably measured directly as the edible plant tissue concentrations of the metal in association with soil metal concentrations in the root zone (NAS/NRC, 2002).

4.5.6.3. *Wildlife*

For most metals, the dietary intake pathway is the main route of exposure for wildlife (NAS/NRC, 2002; see also Section 4.3). However, the incidental ingestion of soil can often contribute a large portion to the majority of the exposure to a wildlife consumer. Because many inorganic metals do not readily accumulate in food (organometalic compounds are excluded from discussion here), highly contaminated soil may result in higher exposures to metals through activities such as grooming fur, preening feathers, consuming soiled prey or forage, burrowing, and taking dust baths. However, canopy feeders would be anticipated to have less incidental soil ingestion and therefore less exposure to inorganic metals than wildlife that consume food that is in more intimate contact with the ground.

The relative importance of the dietary and incidental soil ingestion pathways is dictated by (1) the fraction of total metal available in soil versus that in food and (2) the relative bioavailability of the metal in the soil as compared to metal in food items. Figure 4-7 in Section 4.2.3. shows the relative contribution of food and soil to total metal exposure before accounting for bioavailability. Understanding of the bioavailability of metals in incidentally ingested soils becomes necessary when there is a high amount of metal in the soil that is not taken up by soil organisms (plants or invertebrates). However, the same variables that restrict uptake by plants or other soil organisms act to reduce bioavailability to wildlife that ingest soil directly. Therefore, a qualitative estimate of low relative bioavailability could be made for these soils. Furthermore, data that are generated for human health studies could be used to estimate soil bioavailability for wildlife, acknowledging the uncertainty inherent in such interspecies extrapolations.

Dietary bioavailability. Very little information is available on dietary bioavailability for most wildlife species (see Menzie-Cura and TN&A, 2000), for a review, cited in NAS/NRC, 2002). One of the most significant challenges is that the bioavailability of metals may be influenced by differences in digestive physiology and anatomy across the broad and diverse range of mammalian and avian species. For example, metals present in soils or food may be

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

more or less bioavailable within the gut of an herbivore that relies on fermentation as compared to the comparatively simpler gut of a carnivore that is designed to break down proteins. These gut systems differ in chemistry (including pH) and residence time. The potential differences between species have not yet been explored rigorously. In general, ruminants absorb lower amounts of metals than do monogastric animals such as rats (NAS/NRC, 1980). Some general guidelines are provided for some metals (e.g., lead in NAS/NRC (1980)), and human-derived values can be used as default values in the absence of species-specific data.

Critical body residues (CBRs). CBRs are internal concentrations of chemicals that are correlated with the onset of a toxic response (Conder et al., 2002; Lanno et al., 1998). The use of CBRs reduces uncertainties in ecological risk assessment procedures because they account for site-specific bioavailability and multipathway issues (Van Straalen, 1996; Van Wensem et al., 1994). CBRs can be based on whole-body residues (see below for discussion of this approach in soil invertebates) or concentrations in specific tissues. Tissue-specific critical loads have been established for several species of vertebrate wildlife for lead in liver, cadmium in kidney, and selenium in eggs. See Beyer et al., 1996, for these figures.

4.5.7. Bioavailability in Aquatic Systems

Many factors influence the bioavailability of inorganic metals in aquatic systems. Abiotic (e.g., organic carbon, pH, cations) and biotic (e.g., uptake and metabolism) modifying factors determine the amount of metal that interacts at biological surfaces (e.g., at the gill) and subsequently is taken up. 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 potential impacts because they have differing bioavailabilities, and therefore water quality can dramatically influence the proportion of bioreactive forms of a metal. For many metals in aquatic systems, it is the free ionic form which is believed to be 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 bioavailability for uptake is reduced.

The relationship between speciation and bioavailability is expressed through the FIAM (Campbell, 1995). However, the FIAM is not without limitations, as links between metal speciation and toxicity are complicated and the free metal ion is not always the only bioreactive form. For example, complexed metal, including Cu bound to DOC can be taken up and contribute to toxic impacts and effects (McGeer et al., 2002; Erickson et al., 1996). Although

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

the link between bioavailability of metals and factors influencing speciation (such as pH, temperature, and organic and inorganic anionic complexation) are of prime importance, other abiotic factors, particularly cations, influence metal bioaccumulation and toxicity. Dissolved cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+} can competitively inhibit metal uptake. BLMs, the recently developed integrated toxicity prediction models, have successfully combined abiotic speciation, cationic competition, and bioaccumulation at the presumed site of toxic action (reviewed by Paquin et al., 2002a). The influence of exposure conditions on metal bioavailability is beginning to be understood for some metals, but speciation of metals within the organism is generally less well understood. However, speciation within the organism is likely important for storage, metabolism, elimination, and delivery to and bioavailability at the site of toxic action (Mason and Jenkins, 1995).

It is important to account for bioavailaiblity in relation to exposure conditions when comparing toxicity studies and relating these to natural environments. This includes knowing the species of metal that is likely to be present in the environment. A number of other variables also can influence the outcome of a laboratory toxicity assay, including the acclimation of test animals to the culture conditions (see Section 4.5.2, Acclimation, for further discussion), the natural background concentrations of the metals (including, but not limited to, the metal of interest) in either the test water or the site of concern (see Section 4.5.4, Background), potential interactions of the various metals (see Section 4.5.3, Mixtures), and the potential of the metal to transform to a bioreactive species (see Section 4.1, Environmental Chemistry). The relative compositions of the pretest culture medium and the underlying test medium also should be examined because sudden changes in ionic composition have been shown to cause sufficient stress to sensitize organisms and enhance toxicity (Taylor et al., 1990). This is a necessary prerequisite for successful comparison of effect levels derived from laboratory tests to predicted exposures.

The bioavailability of metals in aquatic systems can vary significantly among taxonomic groups. For example, although most mayflies (*Ephemeroptera*) are generally sensitive to metals, caddisflies (*Trichoptera*) and many stoneflies (*Plecoptera*) are relatively tolerant (Clements et al., 1992). In fact, these species-specific differences in sensitivity to contaminants have motivated the development of numerous indices of water quality that are based on composition of benthic communities (Barbour et al., 1992; U.S. EPA 1989a; Hilsenhoff 1987). Because responses of aquatic organisms to chemical disturbances are usually contaminant specific

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(Slooff, 1983), field assessments of metal effects may be difficult when more than one contaminant is present, and caution is required when using biotic indices to assess effects of complex effluents. In some situations, it may be necessary to either develop chemical-specific indices on the basis of sensitivity to specific classes of contaminants or calibrate metrics used in individual field assessments. For example, metals discharged into a system dominated by highly sensitive taxa (e.g., certain heptageniid mayflies) will have greater effects than the same effluent discharged into a system dominated by tolerant organisms (e.g., certain chironomids). Kiffney and Clements (1996) showed that benthic communities from headwater streams were more sensitive to metals than were communities from mid-elevation streams.

4.5.7.1. *Application*

A variety of methodologies (e.g., hardness adjustments, FIAM, Water Effect Ratio (WER), and aquatic BLMs) can be used to account for differences in concentrations of bioavailable metal species when assessing the effects of metals in aquatic systems (U.S. EPA, 1999b). These bioavailability considerations are important in understanding the exposure conditions of interest and how these relate to toxicity study results. WER determinations can account for site-specific (i.e., dependent on the water quality at a specific location) bioavailability (U.S. EPA, 1994c), although they require the development of animal test data. Hardness adjustments were among the first computational methods to account for bioavailability when applying WQC. FIAM approaches that produce speciation profiles of a metal in an aquatic system provide insight into the relative bioavailabilities of the different forms of metal and the importance of complexation. Several models are available for the calculation of metal speciation in natural waters, including 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 BLM approach further extends bioavialability considerations because it applies the latest information on the chemistry and physiological effects of metals in aquatic environments (Di Toro et al., 2001; Santore et al., 2001; Paquin et al., 1999).

Quantitative Ion Character Activity Relationships (QICARs) can be used to extrapolate from availability and/or toxic data for a metal for which there are data to a metal for which data are limited. The approach is similar to the Quantitative Structure-Activity Relationships (QSARs) that have been used for organic compounds. The QICAR approach was recently

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

integrated into the general context of modern QSAR practices by McKinney et al. (2000), and Weltje (2002) successfully applied it to the lanthanides. The QICAR approach is best applied with a full understanding of the system under study, and the approaches should be validated before application. This approach is but one example of the types of tools that are available but that still need further development to support metals risks assessments for aquatic systems.

In the BLM, chemical speciation is simulated as an equilibrium system that includes complexation of inorganic ions and NOM using the CHemical Equilibria in Soils and Solutions (CHESS) model (Santore and Driscoll, 1995). It includes a description of metal interactions with NOM based on the WHAM (Tipping, 1994). The simulation of biological interactions is based on the binding affinity characteristics measured in gill-loading experiments, originally described by Playle et al. (1993a, b). The biotic ligand (i.e. the gill) is represented as having a characteristic binding site density and conditional stability constants for each of the dissolved chemical species with which it reacts. Predictions of metal toxicity are made by assuming that the dissolved metal LC50, which varies with water chemistry, is always associated with a fixed critical level of metal accumulation at the biotic ligand. This fixed level of accumulation at 50% mortality is referred to as the LA50. The LA50 is assumed to be constant, regardless of the chemical characteristics of the water (Meyer et al., 1999, 2002).

The FIAM and BLM approaches both consider:

- Chemical speciation of the metal and the relative amounts of complexation to inorganic and organic ligands.
- The relative bioavailability of metal species (for example but not limited to the free metal ion) and interactions with other cations that may compete for binding sites of uptake or toxicity.
- Accumulation of metal by the organisms at the site of toxic action.

The BLM approach has been applied successfully to combine the influences of speciation and cationic competition on metal toxicity. (Di Toro et al., 2001; Santore et al., 2001; McGeer et al., 2000; de Schamphelaere and Janssen, 2002, 2004; de Schamphelaere et al., 2002, 2003, 2004; Heijerick et al., 2002a, 2002b, also see example application for Cu below)., The model can distinguish, at least conceptually, metal that will bioaccumulate and cause toxicity from the total metal pools in an organism and the bioavailable metal pool in the exposure media. Themodeling approach has been extended to species such as algae (Heijerick et al., 2002; de Schamphelaere et al., 2003) and *Daphnia* (de Schamphelaere and Janssen, 2002, 2004; de Schamphelaere et al., 2002, 2004), which are toxicologically relevant but more difficult to characterize in terms of accumulation at the site of toxic action.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

While the focus of currently existing BLMs is acute toxicity, the Ion Balance Model (Paquin et al., 2002a, b,c) can be used to extend the applicability of the BLM to evaluate chronic toxicity The Ion Balance model uses the BLM to predict accumulation levels at the biotic ligand and then explicitly represent the degree of the physiological response of the organism to metal exposure over time (i.e., disruption of ionoregulation and gradual loss of plasma sodium). Although the approach, which was initially applied to silver, may ultimately provide a way to predict effects due to metals over varying exposure durations, further development and testing is required. Chronic toxicity models have recently been developed for the impacts of Cu on *Daphnia magna* (de Schamphelaere and Janssen, 2004) and of Zn on fish, *Daphnia* and algae in European Union risk assessments on zinc.

Overall, the BLM approach has wide application in terms of understanding bioavailability in relation to toxicity. It incorporates the influence of speciation in the exposure medium, bioaccumulation and toxic impacts in a robust approach, and has been applied in a variety of contexts. For example, the BLM has recently been incorporated into draft revisions to EPA's water quality criteria for Cu, it has been used in risk assessment and it is being applied as an alternative to the Water Effect Ratio approaches for setting site specific discharge objectives. When considering the application of this approach, as with all models, care should be taken to understand and explicitly account for the assumptions and potential sources of uncertainty.

4.5.7.2. *Limitations*

Novel applications such as the FIAM and BLM have been shown to offer dramatic improvements over traditional approaches such as the hardness equations which depend on the empirical relationship between water hardness and toxicity and the correlation of water quality variables with hardness. While these new approaches offer improvements, there are still many unknowns and uncertainties in relation to bioavailability and the biotic and abiotic influences on metal toxicity. For example, the role of natural dissolved organic matter in bioavailablity and moderating toxicity is not well understood. There are considerable research efforts ongoing currently, and it is likely that our understanding of metal bioavailability and the method for integrating this knowledge into prediction models will improve quickly in the coming years.

> EPA has developed a draft criteria document for copper that incorporates the BLM and will undergo peer review. The draft criterion document is available on the EPA/OST Web page at www.epa.gov/waterscience.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The BLMs that have been and are being developed for a subset of metals (e.g. Cu, Ni, Cd, Ag, Pb, Zn) are based on a limited number of species. BLMs are generally focused on predicting acute toxicity, although there are a few examples of BLMs that predict chronic toxicity, as discussed previously. The development of BLMs to predict chronic toxicity will likely require new knowledge about the combined effects of dietary and waterborne exposure, the mode of toxicity, and the accumulation of metal or dose delivered to the biological site of toxic action. Similarly, acclimation responses, which can influence bioaccumulation at the site of toxicity, are not well understood, and plant and animal species can differ considerably with regard to the forms of metal taken up as well as their relative toxicities. Although these and other issues add complexity to the evaluation, the BLM approach considers metal biogeochemistry; and therefore represents a viable avenue toward understanding and predicting the toxicity of metals.

4.5.7.3. *Example: BLM Application to Development of Copper Aquatic Life Criteria*

The BLM's ability to incorporate metal speciation reactions and organism interactions allows for the prediction of metal toxicity to a variety of organisms over a wide range of water quality conditions. Accordingly, the BLM is an attractive tool for deriving WQC in EPA's water program. Application of the BLM may eliminate the need for site-specific criteria modifications, such as water effect ratios, which are currently used to account for site-specific chemistry influences on metal toxicity. EPA currently is using the BLM to develop a freshwater aquatic life criteria criterion maximum concentration (CMC) for copper. The BLM accounts for inorganic and organic ligand interactions of copper and also considers competitive interactions that influence binding of copper at the site of toxicity. Although a new model is being used, the criterion derivation is still based on the principles set forth in the 1985 guidelines (Stephen et al. 1985). To develop a BLM-based criterion, model predictions of critical accumulations on the biotic ligand (LA50 values) and either LC50 or EC50 values are needed to calculate species mean acute values (SMAVs) and genus mean acute values (GMAVs) as well as to derive a species sensitivity distribution.

4.5.7.3.1. ***Model Input Parameters.*** Much of the aquatic toxicity literature reviewed for the derivation of the copper criterion neither measured nor reported many of the key BLM input parameters. In these cases, the input parameters were estimated. A detailed description of the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

methods used to obtain or estimate these input parameters is included in U.S. EPA (2003a). Briefly, when critical water chemistry parameters were not available, a variety of strategies were employed to find the additional or surrogate data (e.g., authors or lab personnel were contacted, and alternative sources such as studies with similar water quality U.S. Geological Survey's National Stream Quality Accounting Network (NASQAN; http://water.usgs.gov/nasqan/) and the EPA STOrage and RETrieval (STORET; http://www.epa.gov/STORET/) were used). Where sources could not be used to develop geochemical input parameters for the BLM, data were generated using the reported water hardness and regression relationships constructed from NASQAN data.

4.5.7.3.2. ***Quality Ranking of Water Chemistry Input Parameters.*** A ranking system of 1 to 6 was devised to evaluate the quality of the chemical characterization of the test water (but not the overall quality of the study). Studies that included all of the necessary BLM input parameters, based on measurements from either the test chambers or the source water, were assigned a ranking of 1. Rankings of 2 to 4 were assigned to studies that did not measure all parameters but provided reliable estimates of ion concentrations. Studies were assigned a ranking of 5 to 6 when one of the key parameters (DOC, Ca, pH, or alkalinity) was not measured and could not be reliably estimated or if two or more key parameters (DOC, Ca, pH, or alkalinity) were not measured. Only those studies with a rank of 1 to 4 were used to derive the criterion.

As with any modeling effort, the reliability of model output depends on the reliability of the input. Although the input data have been extensively scrutinized and filtered, the reliability of the BLM-derived values developed for copper in this project are subject to the limitations of the input measurements/estimation procedures described above.

4.5.7.3.3. ***Criteria Generation.*** To calculate an acute criterion or CMC, reported acute toxicity values (e.g., LC50s) and individual test water chemistry parameters were used to calculate LA50 values by running the model in the speciation mode. These LA50 values were then "normalized" to a standard water condition by running the model in the toxicity mode and specifying user-defined LA50s. These normalized LC50s were used to calculate SMAVs, GMAVs, and a final acute value (FAV) pursuant to the 1985 guidelines procedure. The FAV represents a hypothetical genus more sensitive than 95% of the tested genera. The FAV was derived from the four GMAVs that have cumulative probabilities closest to the 5th percentile

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

toxicity value for all the tested genera. Inputting this FAV as an LC50 concentration and running the model in speciation mode determines the lethal accumulation associated with the FAV in the standard test water.

The Cu BLM assumes that most of the parameters are invariant for different organisms. Despite the complexity of the modeling framework, the thermodynamic constants used to simulate the inorganic and organic chemical equilibrium reactions are determined by the characteristics of the metal and available ligands. As such, the constants do not change for simulations involving different organisms. Although most BLM parameter values (including the biotic ligand binding constants and site densities) are consistent across organism types, differences in sensitivity across organisms types should still be accounted for. This is accomplished by adjusting the critical biotic ligand concentration (e.g., LA50) values for each species.

This criterion LA50 is programmed into the model as a constant. To derive a criterion for a specific site, the site water chemistry data are input to the model. The model then uses an iterative approach to determine the dissolved copper concentration needed to achieve a Cu-biotic ligand concentration equal to the criterion LA50. This dissolved Cu concentration is, in effect, the FAV based on site water chemistry. The site-specific CMC is this predicted dissolved metal concentration (or criterion FAV) divided by two. The site-specific CCC is the CMC divided by the final acute-chronic ratio.

4.5.7.3.4. ***Next Steps*****.** EPA has developed a draft criteria document that will undergo peer review. When EPA solicits scientific views from the public on the draft criterion document, the model will be made available on the Office of Water web page at www.epa.gov/waterscience. Until the peer review is completed and a final copper criteria document is published by EPA, the procedures described here are draft and subject to change, and the criteria are not considered to be available for use. After completing the copper criteria update, EPA will consider incorporating the BLM into derivation procedures for other metal criteria, such as for silver, cadmium, and zinc. Although the BLM is currently appropriate for use in deriving an updated freshwater copper CMC, further development is required before using it to evaluate a saltwater copper CMC, a CCC, or a chronic value.

Alternative approaches may be considered to establish the database of input parameters for the acute toxicity studies, because the approach described in this document is labor intensive.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Alternatives may include either developing a few high-quality data sets that satisfy the minimum data requirements of the guidelines for a limited set of organisms or developing data sets for known sensitive species. Estimating missing input parameters by relying on statistical techniques or Monte Carlo approaches may also be explored.

4.5.8. Bioaccumulation and Bioconcentration in Aquatic Organisms

Bioaccumulation can be defined as the net accumulation of a metal in a tissue of interest or a whole organism that results from exposure from all relevant sources (e.g. water, food, and sediment). Metal bioaccumulation can apply to the entire organism, including both metal adsorbed to surfaces or absorbed by the organism or to specific tissue. It is usually expressed on a weight (dry or wet)- adjusted basis. Bioaccumulation that occurs under steady-state conditions (i.e., where accumulation remains relatively constant due to uptake being offset by elimination) is often of primary concern in risk assessments. Bioaccumulation of metals is a concern with respect to the accumulating organism when it occurs in the toxicological form(s) and concentrations at the site(s) of toxic action. It also can be indicative of dietary exposure to aquatic organisms at higher trophic levels. While inorganic metals can bioaccumulate in animal and plant tissues, biomagnification across three or more trophic levels is rare.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

The simplest tools for estimating bioaccumulation include direct measures of tissue levels and the derivation of simple relationships between tissue levels and environmental concentrations. These simple empirical relationships have often been expressed as bioaccumulation factors (BAF) or bioconcentration factors (BCF) and various data bases summarize values reported in the literature. It is well recognized, however, that there can be considerable uncertainty associated with the application of literature-derived, bioaccumulation or bioconcentration factors to specific risk assessment situations. In other cases, efforts have been made to establish more detailed mathematical relationships between exposure concentrations and tissue levels. For example, empirical approaches that extend beyond simple factors include the use of regression equations that describe the relationship between exposure and accumulation. Significant advances are also being made on the application of kinetic or steady-state uptake models for describing and predicting bioaccumulation (Reinfelder et al., 1998; Chang and Reinfelder, 2002; Kahle and Zauke, 2003; Wang and Zauke, 2004;). These offer promise for understanding the contribution of differing routes of exposure (e.g., water vs. diet). There is considerable experience in using mechanistic bioaccumulation models for estimating

Biomagnification is defined as an increase in the concentration in an organism from a lower trophic level to a higher trophic level within the same food web due to bioaccumulation from the diet (also see trophic transfer). Biomagnification is expressed as the ratio of the concentration in the organisms of the higher trophic level to the concentration in the organisms of the lower trophic level (i.e., biomagnification factor). Note, however, that biomagnification that is quantified using field data makes an explicit assumption that bioaccumulation results from the diet only, when actually multiple sources may be involved (e.g., water or sediment). Biomagnification factors greater than one indicate biomagnification, while factors less than one indicate no biomagnification or biodilution (see below). Inorganic forms of metals rarely biomagnify across three or more trophic levels.

Biodilution, a decrease in organism concentration with increasing trophic level has generally been more commonly observed when concentrations are evaluated across three or more trophic levels.

Trophic transfer. The transfer of a bioaccumulated substance in a prey species to a predator species via dietary exposure. When the concentration in the predator species is increased relative to the prey, trophic transfer is a form of biomagnification. Trophic transfer is important due to its relationship to dietary toxicity (also called secondary poisoning) in which toxicity is manifest through accumulation in prey species and subsequent dietary exposure to predatory species. Importantly, however, dietary toxicity cannot be directly inferred from an evaluation of trophic transfer alone, but rather the combination of trophic transfer and toxicity information for predator/prey species within an ecologically-linked food web.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

risks of organic chemicals in aquatic systems and it is anticipated that such models will have an increasing role for risk assessments of metals.

Because the simpler empirical approaches such as the BCF and BAF have received much use and attention in the past, they are discussed in further below with respect to applications and limitations. However, the kinetic and steady-state uptake and bioaccumulation models will likely emerge as important approaches.

4.5.8.1. *Scientific Issues with BCF/BAF*

The BCF is the ratio of contaminant concentration in an organism to its concentration in water at steady state conditions and water-only exposures. Metal concentrations are usually expressed on a weight-adjusted, whole-organism basis, and waterborne metals may be expressed as total or dissolved metals. BCFs have been developed primarily with hydrophobic organic chemicals in aquatic systems, but similar such accumulation factors have been applied to other matrices (e.g., sediment and soils) for both organic chemicals and metals. Strictly speaking, metal bioconcentration in sediment and soil systems is the net accumulation of a metal in or on an organism from pore water only. Hence, in sediment and soil, the denominator for the BCF ratio should comprise the pore water concentration of metal, not the total metal concentration in the sediment or soil. In the broadest context, the BAF is the ratio of a contaminant concentration in an organism to that in a specified medium at steady state in situations where the organism is exposed to multiple environmental media.

Although BAFs and BCFs are calculated in a similar manner, the interpretation is slightly different with metal accumulation in organisms arising from water only for BCFs and from both water and dietary sources for BAFs. For aquatic organisms, BAFs are derived from measurements in natural environments, and BCFs are nearly always measured under laboratory conditions where exposure can be effectively limited to the water column. Unless metal concentrations in pore water serve as the denominator for the ratio, soil and sediment BAFs are usually termed BSAFs. Concentrations are usually measured on a total-metal and weight-adjusted whole-organism (or tissue) basis.

Toxicological bioaccumulation is the fraction of the metal that bioaccumulates and is distributed to receptors at sites of toxic action (Figure 2-2). For metals, this would include reactions with target proteins or other receptors that result in toxicity but not interactions with metallothionein and other metal-binding ligands or incorporation into granules that make metals

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

unavailable for interactions with target molecules. This fraction is conceptual in nature and difficult to measure in practice; it is akin to the minimal effective dose measured in blood that is often used in medicine for assessing therapeutic effects. It could be conceptually defined as a toxicological bioaccumulation fraction or the ratio of total metal concentration in an organism to the metal concentration at the site(s) of toxic action.

As discussed in more detail in McGeer et al 2004, there are fundamental differences in the physical, chemical and toxicological properties of inorganic metal substances and organic substances, such that the BAF/BCF model would not apply to the former. The success of the BAF/BCF model as a valid indicator of the environmental and toxicological behavior of neutral organic substances is due to their hydrophobic/lipophilic chemical properties, and this has important consequences for application to inorganic metals. Many of the assumptions and characteristics of the BAF/BCF model openly conflict with the physical, chemical, biological, and toxicological realities associated with inorganic metal substances. For example, the BAF/BCF model works well for neutral organic substances because uptake of lipophilic substances into biota occurs via simple passive diffusion. However, uptake of the vast majority of inorganic metals is a physiological process, which occurs via a number of specific routes, most of which involve saturable transport kinetics. The degree of uptake and ultimate internal fate of inorganic metals is strongly influenced by ligand binding and receptor site competitive interactions which control metal availability and/or transfer processes, and cannot be reliably represented by a simple partitioning between water and organism. As a result of the differences explained below, simple application of these models is meaningless in assessing acute and chronic toxicity (adapted from McGeer et al., 2004):

- The principal theoretical features of the BAF/BCF model that make it applicable to neutral organic substances also make it inapplicable to inorganic metal substances. These factors produce an inverse relationship between BAF/BCF and exposure concentration; this has been observed for both essential metals and nonessential metals.

- The approach of using one simplified bioaccumulation model (BCF and BAF) and applying it to inorganic metals ignores the basic physical and chemical differences

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

between organic and inorganic substances and is not supported by theoretical and empirical weight of evidence.

- Based on the inherent assumptions of the BCF and BAF model and on the environmental and toxicological behavior of the organic substances from which they were developed and validated, for the vast majority of inorganic metals evaluated, the scientific basis for broad application of the BAF/BCF model is lacking in the context of hazard assessment.

- The complexity of assessing and predicting the bioavailability and bioaccumulation of metals in aquatic systems arises from many factors including:
  - Essentiality of some metals resulting in a "U"-shaped dose response curve.
  - Variation in assimilation efficiency for different species of metal, for different biota and at different sites of uptake.
  - Ability to modulate uptake at the various sites of uptake.
  - Contributions of different routes of entry to the metal body burden and effects.
  - Ability to sequester, store, detoxify and eliminate bioaccumulated metals.
  - All metals will bioaccumulate to some degree without impacts as a result of exposure to natural background concentrations

- Based on reviews (e.g., McGeer et al., 2003), it would appear that for the vast majority of the metal/taxonomic group combinations assessed, the assumptions regarding the independence of BCF/BAF with exposure concentration and proportionality of hazard with increasing BCF/BAF do not hold true.

- The latest scientific data on bioaccumulation do not currently support the use of BCF and BAF data when applied as generic threshold criteria for the hazard potential of inorganic metals (e.g., for classification as a "PBT" chemical).

- In cases where the use of BCF/BAF data are being considered, a careful evaluation of existing data for metals that formally documents the extent to which values represent bioaccumulation linked to toxic impact (both direct and indirect) and the resulting

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

uncertainty introduced by concentration dependency and other aspects of the BCF/BAF data should be done.

- Moving from the current situation to a revised, improved, and validated set of criteria and/or methodologies for assessing metal hazards and risks presents a number of options and challenges, as currently there would appear to be no clear alternatives ready for application.

- BCFs for metals will not be absolute values, but will vary widely with both the specific exposure circumstances/conditions as well as the status/age/condition of the particular organism measured. This applies to all substances, organic and inorganic, although the relative scale of the uncertainty added is greater for inorganic substances.

The Organization for Economic Co-operation and Development (OECD) has published guidance for the hazard classification of chemical substances (OECD, 2001). The hazard classification schemes presented in the OECD guidance incorporates, among other parameters, evidence of bioaccumulation as a basis for hazard ranking. The OECD guidance recognizes the shortcomings associated with the use of BAF/BCF data as a surrogate for the hazard potential of metals, and therefore cautions that metals should be assessed on a case-by-case basis rather than recommending the application of the simple bioaccumulation model (BAF/BCF). The principle features of the BAF/BCF model that make it applicable as a surrogate for acute and chronic toxicity to neutral organic substances also make it inapplicable to inorganic metal substances as discussed above and in McGeer et al. (2004).

The phenomena described above regarding the limitations of the BCF/BAF model also have a bearing on the use of BCFs and BAFs in national-level assessments (e.g., water quality criteria and national-scale risk assessments) in addition to site-specific assessments. For example, variability in BCFs and BAFs caused by an inverse relationship of BCF with exposure concentration can confound the application of BCFs in risk assessments, the extent to which depends in part on the magnitude of this relationship (i.e., its slope) and the extent of extrapolations made (i.e., extrapolation of BCFs across differing exposure concentrations and species). For organic chemicals, generic normalizing factors have been shown to reduce variance in BAFs due to bioavailability differences (e.g., normalizing to organic carbon and

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

lipid; see Burkhard et al., 2003). However, analogous normalizing factors have yet to be developed and widely applied in the context of BAFs or BCFs for metals, although some progress has been made with relating accumulation parameters to body weight (Hendriks and Heikens, 2001) or permeable surface area in the case of the amphipod, *Gammarus zaddachi* (Wang and Zauke, 2004). Simple normalizing factors can be confounded by the fact that animals and plants have evolved physiological and anatomical means for regulating and or storing internal concentrations of metals and the species-dependent specificity of these mechanisms. Regulation of metals by biota can actually result in decreased apparent BAF/BCF factors with increasing exposure concentrations. Thus, a fundamental understanding of such mechanisms is important for reducing the uncertainties associated with interpreting tissue residues. The mere presence of a metal in a plant or animal does not mean it is at a site of toxic action. In summary, caution should be exercised when using published BAF and BCF values to make judgements about resultant tissue levels of metals in animals and plants. Where this is found to be necessary as an initial, screening level of assessment, the associated uncertainties should be identified and discussed with respect to their potential impact on the risk estimates and resultant decisions.

In situations where a decision has been made to employ a BAF or BCF factor, there may ways to reduce some of the uncertainty. One idea involved subtracting "normal" accumulation from the calculation of the BCF. This involves separating the portion of metal that bioaccumulates from exposure under "normal" or background conditions from that portion that occurs as a result of exposure to elevated levels of metals (McGeer et al., 2003). The ACF value also accounts for the accumulation of essential metals required for physiological function. These ACF values were dramatically lower than BCF values (illustrating the importance of normal bioaccumulation) for some metals, particularly essential metals. However, for most metals ACFs still varied with exposure concentration and were not viewed as a sufficient replacement to the BCF (McGeer et al., 2003).

Another approach that may reduce uncertainty caused by concentration dependency of BCFs and BAFs involves limiting the selection and application of BCF and BAF values to concentration ranges that more closely correspond to toxicological thresholds. For example, limiting the calculation of BAF and BCF values to concentrations that approximate the applicable water quality criterion has also been suggested as a method for reducing the uncertainty around BCF and BAF values in situations where concentration dependency is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

evident. This would account for bioaccumulation at an exposure level where concern over bioaccumulation might be expected. This approach has limitations (McGeer et al., 2004) and does not appear to reduce the overall variability associated with BCF and BAF measurements when evaluated across broad classes of organisms. An additional issue for this approach is that WQC reflect some of the more sensitive organisms, whereas the BCF and BAF measurements are not necessarily from these same organisms and include data from biota that may not be as sensitive to chronic effects. Therefore, as a modifier for broad-based application, this variation of the BCF/BAF methodology does not appear to explain variability. However, on a site-specific basis where toxicity thresholds and species are better characterized, this approach may have value in reducing uncertainty. As already noted, caution should be exercised with any of the BAF or BCF applications.

4.5.8.2. *Bioaccumulation in Relation to Dietary Toxicity*

Discriminating between metals that have the potential to cause effects via trophic transfer and metals that do not is another approach that might be useful in distinguishing between metals, based on bioaccumulation and impacts. Metals taken up and stored within an organism may not cause direct effect to that organism but may be bioavailable to organisms in the next trophic level that feed on it. Bioaccumulation of metals in prey organisms may be quite high, especially in organisms such as high volume filter feeders and those that accumulate elevated levels of metals, for example, those that store detoxified forms. Metals that bioaccumulate to levels in prey organisms that cause impacts in predatory organisms are clearly important issues to address however, there is a general lack of understanding of the potential for toxicity.

A prey organism with a high concentration of a particular metal represents a potential opportunity for the trophic transfer of the metal from an enriched source to a predator at the next trophic level. The form of detoxified storage of that accumulated metal in the prey species has a significant effect on the potential assimilation of that metal by the predator (Wang and Fisher, 1999). For example, Nott and Nicolaidou (1990) have shown that the bioavailability to neogastropod mollusc predators of metals present in detoxified metalliferous granules in prey varies among metals and with type of granule; thus the zinc-rich pyrophosphate granules accumulated in barnacles are not digested in the digestive tract of the predator *Nucella lapillus* and are therefore not bioavailable to that predator. Similarly the physico-chemical form of accumulated cadmium in the oligochaete *Limnodrilus hoffmeisteri* is critical in the assimilation

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of cadmium by a predator, in this case the decapod *Palaemonetes pugio* (Wallace et al., 1998; Wallace and Lopez, 1997). Other studies have indicated that lead bioaccumulated in mussels and stored in a detoxified form within the soft tissues of the mussels is bioavailable and may cause impacts (Regoli and Orlando, 1994). The potential effects of food preparation (cooking) on metal bioavailability should be considered when assessing risks to human consumers.

Currently there are no standardized tools for incorporating the potential impact of dietary exposure into assessments. Research efforts are focusing on the relative importance of: dietary pathways in relation to waterborne exposures, transfer from sediments into food chains, the potential of bioaccumulated to cause impacts in consumer organisms. One example of an approach that illustrates how exposure, bioaccumulation and trophic transfer can be linked is illustrated below.

A general approach to account for potential impacts arising from trophic transfer would be to link bioaccumulation in prey items to exposure in the water column as well as potential impacts in consumers. One methodology to achieve this is to integrate tissue burden to toxicity relationships (prey: predator interactions) with exposure to bioaccumulation relationships (e.g., BCF and BAF values). A theoretical example of this approach, developed by Brix et al. (www.epa.gov/ncea/raf/pdfs/metals/sumryrprt_metals.pdf) is shown in Figure 4-9.

Within the context of this approach, it would be necessary for relevance to ensure that the species being considered were linked within trophic food webs (i.e., the exposure to bioaccumulation relationship was for prey items being consumed by the predators that are sensitive to trophic transfer). Some data already exists to begin these evaluations. For example, it is possible to derive the water concentrations necessary to produce impacts via dietary exposure (see Brix et al. reference above) and site-specific case studies would be valuable in illustrating, testing, and validating these relationships. The potential benefits from this approach would be reducing the uncertainty from extrapolations across exposure concentrations currently being made with metals BCF/BAF data. Also, there would be an ability to link impacts through to waterborne metal concentrations. However, particularly if BCF and BAF data is used, this approach would bring with it the inherent uncertainty associated with predicting tissue metals burdens (e.g., the high variability) and the inability to account for geochemical influences on uptake and accumulation. Ensuring that the local site specific factors that influence the bioaccumulation and the expression of impacts are understood and recognized would be important, to ensure for example that criteria and guideline values were not set at existing

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

background levels. Two regression relationships, one for exposure and bioaccumulation (green line) and the other for bioaccumulation to dietary toxicity thresholds (blue line) are used to line exposure and dietary impacts.

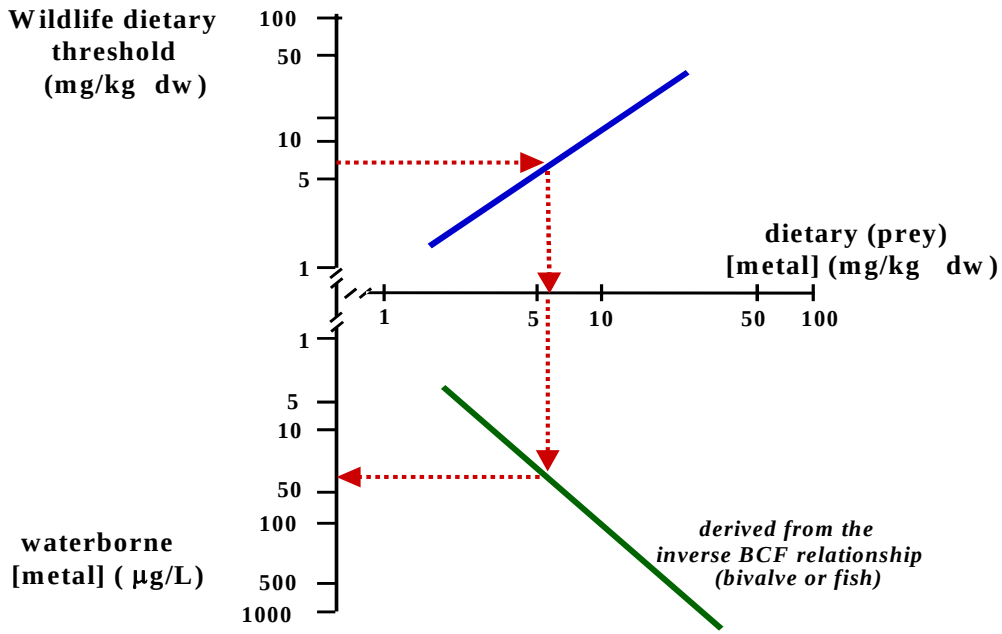

Figure 4-9. Linkages between dietary toxicity threshold, bioaccumulation in prey organisms and waterborne exposure.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.8.3. *Alternatives to Tissue Burdens and Bioaccumulation*

A key parameter that a bioaccumulation measure should be validated against is chronic toxicity. Because bioaccumulation criteria within the context of persistent, bioaccumulative, toxic substances are used as indicators of chronic toxicity (Franke et al., 1994; OECD, 2001), validation of linkages to chronic metal toxicity would provide confidence in their use and application. A number of key issues should be addressed when considering bioaccumulation of metals in relation to the potential for chronic impacts, and these add uncertainty to the interpretation of data. However, unlike the substances that the PBT concept was originally developed for, there is often substantial information on the chronic toxicity of metals.

In some regards, our ability to understand and interpret chronic metal toxicity is as advanced, or possibly more advanced, than metal bioaccumulation. Therefore, rather than trying to derive and validate a surrogate for the chronic impacts of metals, it might, in some cases, be feasible to eliminate bioaccumulation and only consider chronic toxicity data. The development of a criterion based on chronic toxicity could be based on a variety of approaches, all of which will require a modified framework for consideration as BCFs, BAFs, and bioaccumulation would be replaced. Despite the challenges associated with this degree of change, it is worthy of consideration.

4.5.9. Bioaccumulation in Terrestrial Organisms

For terrestrial ecosystems, the concept of bioaccumulation is intended to capture the potential for two ecologically important outcomes: (1) direct toxicity to plants and wildlife and (2) secondary toxicity to animals feeding on contaminated plants and animals. This approach captures the potential for trophic transfer of metals through the food web, so total exposure can be calculated, including dietary intake as well as intake from contaminated environmental media (soil and water). For vegetation, the BAF (or BSAF) is defined as field measurements of metal concentration in plant tissues divided by metal concentration in soil (or soil solution); the BCF is defined as the same measurement carried out in the laboratory (Smolders et al., 2003).

Data applicability is directly related to which tissue is sampled and how it is processed. BAFs for plants include metals aerially deposited on leaves as well as those in soil particles adhering to roots. Such metals will not be part of BCFs, which frequently are determined in hydroponic culture. Similar differences between BCFs and BAFs apply for earthworms exposed in laboratory studies using the filter paper substrate protocols. Furthermore, BCFs with

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

earthworms may not include additional feeding of the animals during the study. Additionally, field studies are reflective of chronic exposures, whereas BCFs may be calculated from shorter time frames. For birds and mammals, whole-body BAFs generally are not calculated, except for small mammals such as rodents (Sample et al., 1998b). Rather, concentrations in target tissues are measured for comparison with critically toxic levels (Beyer et al., 1996).

The BAFs for metals by soil invertebrates and most plants are typically less than 1, although they usually are based on the total metal in soil and tissue. BSAFs expressed in this manner may be suitable for comparisons of metal uptake within the same soil type, but they would be misleading if soil bioavailability factors (e.g., pH and organic carbon) differ. Unfortunately, the literature database is populated almost entirely with BAFs derived from measurements of total metal. Furthermore, bioaccumulation is not a simple linear relationship. Uptake is nonlinear, increasing at a decreasing rate, as medium concentration increases. Reliance on incorrect relationships of the bioavailable portion will be trivial compared to the error associated with BAFs at high concentrations. In the future, a ratio of total metal in the organism to some measure of the bioavailable fraction of metal in the soil (e.g., free ion concentration or weak salt extractable) should be used for expressing a BSAF that allows comparison among different soils. An alternative approach currently under study is to use a multivariate statistical model to look for patterns of uptake of multiple metals to predict the potential bioconcentration of one metal of particular interest (Scott-Fordsmand and Odegard, 2002).

4.5.9.1. *Models for Bioaccumulation in Soil Inverterbrates*

4.5.9.1.1. *Application*

4.5.9.1.1.1. *<u>Univariate models</u>*. The bioaccumulation of metals in soil organisms cannot reasonably be modeled from information based solely on soil concentrations. Therefore, models for the prediction of metal bioaccumulation by soil invertebrates are primarily empirical in nature, describing relationships between metal body burdens in oligochaetes and collembola, soil metal concentrations, and soil physical/chemical characteristics. Statistical relationships have been established using univariate and multiple regression

The bioaccumulation of metals in soil organisms cannot be modeled from information based solely on soil concentrations. Two types of models are available to help describe the relationships between metals body burden and soil parameters: (1) ***univariate models*** that describe statistical relationships between body burdens, soil metal concentrations, and soil physical and chemical properties; and (2) ***multivariate models*** that explain BAFs as a function of soil properties.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

approaches. 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 are widely used as a first approximation. However, these models are not specific to soil type and therefore do not account for bioavailability factors such as pH, clay content, or cation exchange. Furthermore, they do not adequately predict Cr or Ni uptake.

4.5.9.1.1.2. ***Multivariate models.*** Multivariate models also are available (Peijnenburg et al., 1999a, b) for *Eisenia andrei* and *Enchytraeus crypticus* that explain BAF as a function of soil characteristics. The soil parameters that generally contributed the most to explaining the variance between uptake rate constants and BAFs were pH (for Cd, Zn) and also CEC (for Pb) and clay content (for Cd). Similar studies are needed for describing relationships between soil physical/chemical characteristics and metal bioaccumulation in other groups of soil invertebrates such as collembola and isopoda. Until these are available, the models for earthworms and enchytrids can be applied to other groups, although the added uncertainty should be acknowledged.

Path analysis has been suggested as an alternative for multiple regression in describing these relationships. It partitions simple correlations into direct and indirect effects, providing a numerical value for each direct and indirect effect and indicates the relative strength of that correlation or causal influence (Basta et al., 1993). Bradham (2002) used path analysis and backwards stepwise regression analysis to derive statistical models capable of predicting uptake and effects of As, Cd, Pb, and Zn in earthworms as a function of soil properties.

Saxe et al. (2001) described a model for predicting whole-body concentrations of Cd, Cu, Pb, and Zn in *Eisenia andrei* as a function of pH, soluble metals in the soil at gut and environmental pH, and soluble organic carbon in soil extracts. The model also includes parameters that characterize the ability of worms to regulate the metal body burden, whether metal uptake is via the epidermal or gut surface and whether the metal is essential. The model has been validated against a series of Dutch soils and is very good at correctly predicting metal accumulation.

4.5.9.1.2. ***Limitations.*** Bioaccumulation of organic substances is typically modeled using a One-Compartment, First-Order Kinetics (1CFOK) model. However, most of the assumptions of the model are violated when applied to bioaccumulation of metals by soil invertebrates. Soil

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

invertebrates are not exposed to a constant concentration of metals in the soil over space and time, making it difficult to accurately define exposure. Sufficient data exist on the metabolism of metals to show that all pools of metal taken up by the soil invertebrates are not equally available for depuration (some are actually never depurated and are released only when the organism dies), making a 1CFOK model an inaccurate approximation.

Metal concentrations do not reach a steady state that is proportional to external (i.e., soil) concentrations. This is similar to the situation in aquatic systems where metal bioaccumulation is a function of water concentration. Internal essential metal concentrations are regulated and remain relatively constant over a wide range of soil metal concentrations. Only when normal regulatory mechanisms are overwhelmed do internal levels of essential metals increase. Accumulation of nonessential metals also violates the assumption of steady state, as organisms have evolved mechanisms for the detoxification of nonessential metals that involve the internal accumulation of the metal in forms that are not toxic to the organism (e.g., incorporation into inorganic granules or binding to organic molecules to form metal ligands such as metallothioneins).

4.5.9.2. *Critical Body Residues*

CBRs are an extension of the concept of bioaccumulation to internal concentrations of metals that are correlated with some toxic response and hence represent toxicological bioavailability (Conder et al., 2002; Lanno et al., 1998). Use of CBRs in appropriate species may reduce uncertainties in ecological risk assessment procedures (Van Straalen, 1996; Van Wensem et al., 1994). However, only a few CBRs have been developed in soil invertebrates for metals. Crommentuijn et al. (1997, 1994) and Smit (1997) established CBRs for sublethal effects for Cd and Zn, respectively, in the springtail (*Folsomia candida*). Conder et al. (2002) demonstrated that effects of Cd in earthworms (*Eisenia fetida*) are

Knowing the species of metal that is likely to be present in the environment is important for extrapolating results from laboratory tests to natural settings. Laboratory studies are often done under simplified environmental conditions (compared to the natural environment) that may enhance aquatic bioavailability. Conversely, these studies frequently do not include potential effects of dietary metal exposure.

In addition to abiotic factors that can influence metal bioavaiability, other variables may potentially affect the outcome of laboratory toxicity assays and should be considered in interpretation of data. These include acclimation of test animals to culture conditions, natural background concentrations of the metal (including, but not limited to the metal of interest), potential interactions of the various metals, and potential transformations to bioreactive species. The similarity of the pretest culture medium to the underlying testing medium also should be considered.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

correlated with concentrations of the metal in the solid phase of the worms (i.e., the pellet fraction, following homogination and centrifugation). If future research can isolate the fraction of an invertebrate that represents toxicological bioavailability, then it may be possible to estimate a toxicological BSAF representing a relationship between a specific fraction of metal that accumulates in the organism and a measure of chemical bioavailability in the soil. Until then, CBRs based on whole-organism analyses are a reasonable approximation for use in ecological risk assessments.

4.5.10. Sediment Toxicity - Equilibrium Partitioning Approach for Metals

4.5.10.1. *Rationale for Use of EqP Benchmarks*

Toxic pollutants in bottom sediments of the nation's lakes, rivers, wetlands, estuaries, and marine coastal waters create potential for continued environmental degradation even where water column concentrations comply with established human health and aquatic life WQC. In addition, contaminated sediments can be a significant pollutant source that may cause water quality degradation to persist even when other pollutant sources are stopped (U.S. EPA 1997d,e,f; Larsson, 1985, Salomons et al., 1987; Burgess and Scott, 1992).

Because of their widespread use and associated environmental releases, metals such as cadmium, copper, lead, nickel, silver, and zinc are commonly elevated in aquatic sediments. Various types of sediment guidelines have been proposed for assessing the potential effects of these metals on benthic invertebrate communities. Many of these involve empirical correlations of metal concentrations in sediment with associated biological effects (e.g., sediment toxicity); these include ER-M, ER-L, TEL and PEL, SLC, AET and others (Sullivan et al., 1985; Persaud et al., 1989; Long and Morgan, 1990; Ingersoll et al., 1996; MacDonald et al., 1996). Most of these approaches use measures of total metal in sediment, and do not account for differences in bioavailability of metals among sediments. Nevertheless, when examined across large data sets, these empirical guidelines do show relationships between concentrations of total metal and biological effects. However, a limitation to these empirical approaches is that the causal linkage between the measured concentration of metals and the observed toxicity cannot be established, in part because of the procedures used to derive correlative values and because values derived are based on total rather than bioavailable metal concentrations. That is, for any given total metal concentration, adverse toxicological effects may or may not occur, depending on the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

physicochemical characteristics of the sediment of concern (Tessier and Campbell, 1987; Luoma, 1989; Di Toro et al., 1990).

An alternative to empirical approaches is equilibrium partitioning (EqP) theory. The EqP approach is intended to predict concentrations that will or will not cause adverse effects based on an understanding of the factors that control metal bioavailability in sediments and the relationship between that bioavailability and biological effects. For cationic metals (e.g., cadmium, copper, lead, nickel, silver, and zinc), these factors include the presence of acid volatile sulfides (AVS), which form insoluble metal sulfides that are believed to have low biological availability. Beyond AVS, particulate organic carbon (POC) and iron and manganese hydroxides in sediment, and dissolved organic matter (DOM) in interstitial water are also believed to influence metal bioavailability in sediment. By recognizing differences in bioavailability among sediments, the intent of the EqP approach is to produce guideline values that are applicable across a wide variety of sediments and represent causal relationships between specific chemicals and sediment toxicity.

In 1987, EPA reviewed proposed approaches to developing numerical sediment quality guidelines (Chapman, 1987). All of the approaches reviewed had strengths and weaknesses, and no single approach was found to be applicable for the derivation of sediment benchmarks in all situations (U.S. EPA, 1989d). The EqP approach was selected for further development because it presented the greatest promise for generating defensible national chemical-specific sediment benchmarks applicable across a broad range of sediment types. While the Agency has never adopted formal sediment quality criteria, the technical development of sediment quality guidelines was pursued and has resulted in the publication of several numerical guidelines (See http://www.epa.gov/nheerl/publications/). These guidelines are called “EqP sediment benchmarks” (ESBs) and are numerical concentrations for individual chemicals or mixtures of chemicals derived using the EqP approach. As described below, these are intended to be concentrations below which there should not be direct toxicity to most benthic organisms as a result of the chemical or chemicals addressed in the guideline.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.10.2. *Application of the EqP Approach*

As originally proposed, the EqP approach for copper, cadmium, lead, zinc, nickel, and silver focused on AVS as the principal partitioning phase. Because these metals form sulfides that are highly insoluble, toxicity from these metals is not expected if there is sufficient sulfide available to bind all available metal. Because some metals in sediment are present in mineral forms that are not highly reactive, the metal concentrations to which the sulfide concentration is compared is not the total metal in sediment, but the metal extracted simultaneously with the sulfide, and is therefore referred to as simultaneously extracted metal (SEM). Because cadmium, copper, lead, nickel, and zinc are divalent metals, 1 mol of each metal can bind with 1 mol of AVS. The molar concentrations of these metals are compared with AVS on a one-to-one basis. Silver, however, exists predominantly as a monovalent metal, so that silver monosulfide (Ag_2S) binds 2 mols of silver for each mol of AVS. Therefore, SEM Ag will represent the molar concentration of silver divided by two, [Ag]/2, which is compared with the molar AVS concentration. Thus, the solid-phase AVS ESB is defined as:

$$\Sigma_i [SEM_i] \leq [AVS]$$

where:

$$\sum_i [SEM_i] = [SEM_{Cd}] + [SEM_{Cu}] + [SEM_{Pb}] + [SEM_{Ni}] + [SEM_{Zn}] + 1/2[SEM_{Ag}]$$

When this sum is less than the molar concentration of AVS, no toxicity is expected because there is sufficient sulfide to bind all SEM. Results of calculations using chemical equilibrium models indicate that metals act in a competitive manner when binding to AVS. That is, the six metals will bind with AVS to form their respective sulfides in the order of their increasing solubility: silver, copper, lead, cadmium, zinc, and nickel. Therefore, they should be considered together. There cannot be a guideline just for nickel, for example, because all the other metals may be present as metal sulfides and therefore, to some extent, as AVSs. If these other metals are not measured as a mixture, then the $\sum$SEM will be misleadingly small, and it might appear that $\sum$[SEM]<[AVS] when in fact this would not be true if all the metals were considered together. It should be noted that EPA currently restricts this discussion to the six metals listed above; however, in situations where other sulfide-forming metals (e.g., mercury) are present at high concentrations, they also should be considered.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

While the SEM-AVS comparison has been found effective for predicting when metals in sediment will not cause toxicity, the presence of excess SEM above AVS does not always portend toxicity. This is, at least in part, because other components of sediments can also reduce the bioavailability and toxicity of metals. To address these additional factors, a second component of the metal mixture ESB was developed: the interstitial water benchmark. The concept behind the interstitial water component is that even if there is excess SEM above AVS in a sediment, if there is sufficient additional binding available to maintain non-toxic concentrations of metals in the intersititial water, then the sediment should not be toxic, despite the excess SEM. The aggregate toxicity of metals in the interstitial water is assessed by dividing the concentration of dissolved metal in interstitial water by the final chronic value from the EPA water quality criterion for the protection of aquatic life. This ratio is called the Interstitial Water Benchmark Unit (IWBU), and these are summed across all of the metals (using an assumption of addivity, as described in Section 4.5.3); if the sum is less than 1, then the interstitial water-phase ESB is met, and toxicity is not expected. Mathematically, this equates to:

$$\Sigma[M_{i,d}]/\,[FCV_{i,d}] \leq 1$$

where:

$$\sum_i([M_{i,d}]/FCV_{i,d}) = \sum_i([M_{Cd,d}]/FCV_{Cd,d}) + \sum_i([M_{Cu,d}]/FCV_{Cu,d}) + \sum_i([M_{Pb,d}]/FCV_{Pb,d}) + \sum_i([M_{Ni,d}]/FCV_{Ni,d}) + \sum_i([M_{Zn,d}]/FCV_{Zn,d})$$

For freshwater sediments, the FCVs are hardness dependent for all of the divalent metals under consideration, and thus should be adjusted to the hardness of the interstitial water of the sediment being considered. Because there are no FCVs for silver in freshwater or saltwater, this approach is not applicable to sediments containing significant concentrations of silver (i.e., ΣSEM>AVS). Because silver has the smallest solubility product and the greatest affinity for AVS, it would be the last metal to be released from the AVS or the first metal to bind with AVS. Therefore, it is unlikely that silver would occur in the interstitial water of any sediment with measurable AVS (Berry et al., 1996).

When used together, the overall metal mixture ESB is met if either the SEM-AVS or interstitial water ESBs are met. Further, both guidelines are no-effect guidelines, in that they predict the absence of toxicity if they are met. Though the probability of toxicity is higher if both components of the ESB are exceeded, and this probability increases as the magnitude of

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

exceedance increases, failing to meet the ESB does not imply that toxicity will necessarily occur. This is because neither the SEM-AVS or interstitial water components address all factors that may reduce the bioavailability and toxicity of metals in sediment. Site-specific toxicity testing may be advisable to refine assessments for specific sites.

4.5.10.3. *Enhancements to the Metals ESB*

The AVS guideline is a "no effects" guideline; that is to say that if the guideline is not exceeded, the sediments should not be toxic due to the metals included in the guideline, but an exceedence of the guideline does not necessarily mean that the sediments will be toxic due to the presence of those metals. One way to reduce the uncertainty of a prediction of toxicity is to normalize for the fraction of organic carbon in the sediment and use $\sum$SEM-AVS)/f_{OC} for the solid-phase guideline. The use of this guideline is described in the draft metals ESB (EPA 2002f).

A refinement of this organic carbon correction has been proposed by Di Toro et al. (2004, submitted). In this analysis, organic carbon partition coefficients are calculated for each metal and used to estimate combined AVS-organic carbon partitioning. Although this approach has not been widely applied as yet, it has a strong theoretical basis, and initial applications suggest that it can strengthen the ability of EqP to predict metal toxicity (rather than just non-toxicity) in sediments.

The metals ESB currently applies to only six metals: cadmium, copper, lead, nickel, silver, and zinc. However, AVS can also be used to predict the lack of toxicity in sediments due to chromium because the presence of AVS in sediments is indicative of reduced sediments. Chromium is present primarily in its reduced form (CrIII) in reduced sediments, and in this form it is much less toxic and bioavailable than the oxidized form of chromium (CrVI) (Berry et al., in prep.). The use of AVS in the prediction of the lack of chromium toxicity in sediments will be described in an addendum to the metals ESB.

4.5.10.4. *Endpoints of Concern*

The metals ESB should be viewed as an approach, as opposed to a specific number. The ESB calculates a concentration in sediment that will correspond to a given toxicological endpoint using partitioning theory. However, the correspondence of the benchmark is variable, depending on which toxicological endpoints are selected. The FCVs from the metals WQC are

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

used in the ESB as examples because they are familiar and provide a widely accepted level of protection. Other toxicological endpoints could be chosen, however, if a different level of protection was desired. For example, the water-only, chronic no-effect concentration for a threatened or endangered species might be used as the toxicological endpoint. EqP theory could then be used to calculate a sediment concentration that would be protective of that species.

4.5.10.5. *Limitations*

It should be emphasized that the metals ESBs are intended to protect benthic organisms from the direct effects of these *six metals* in sediments that are permanently inundated with water, intertidal, or inundated periodically for durations sufficient to permit development of benthic assemblages. They do not apply to occasionally inundated soils containing terrestrial organisms. These benchmarks do not address the possibility of bioaccumulation and transfer to upper-trophic-level organisms or the synergistic, additive, or antagonistic effects of other substances.

The EqP approach to metal assessment has been questioned on several technical issues, such as whether it applies to organisms that live in oxygenated burrows, whether it adequately accounts for ingestion of sediment, and whether it is appropriate to use bulk sediment chemistry to represent responses to microenvironments that exist in bedded sediment. Many of these issues are difficult to address in a comprehensive manner, and more study will be required to fully evaluate them. In the interim, it should be noted that there is a considerable body of experimental data supporting the EqP approach to metals (Berry et al. 1996; Hansen et al. 1996; Di Toro et al. 2004; EPA 2002f), and these data include tests with organisms with varying life histories, that use irrigated burrows, and that ingest sediment. While this does not prove that the criticisms above are not legitimate, it provides support for continuing to apply the EqP approach as a reasonable representation of metal toxicity in sediment, at least until a superior approach is developed.

Because AVS is a product of microbial activity, AVS can vary seasonally with changes in microbial activity. The degree to which such cycling can affect the potential risk from metals in sediments is unclear but should be considered in sampling programs designed to assess SEM-AVS.

Because metals bound to sulfide do not appear to be sufficiently bioavailable to cause toxicity in sediment toxicity tests, one would not expect bioaccumulation of metals in sediments

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

with more AVS than SEM. However, several studies have found bioaccumulation of metals even when excess AVS is present (Ankley et al., 1996). This has caused considerable debate about the appropriateness of SEM-AVS for assessing metal toxicity in sediments (e.g., Lee et al., 2000), because it suggests that metal bioavailability may not be effectively represented by SEM-AVS analysis. However, there is a large number of studies indicating that toxic effects of metals are absent in sediments when SEM is less than AVSs, even when bioaccumulation is observed. This suggests that the bioaccumulated metals may not be toxicologically available or of sufficient concentration in the organism to cause effects. In addition, these metals do not biomagnify to higher trophic levels in aquatic ecosystems (Suedel et al., 1994). Therefore, an ESB based on the difference between the concentrations of SEM and AVS still appears appropriate for protecting benthic organisms from the direct effects of sediment-associated metals, but not for protecting against metal bioaccumulation.

4.5.10.6. *Use and Implementation*

In practice, the sediment benchmarks for these six metals are not exceeded, and benthic organisms are sufficiently protected (defined in this case as the level of protection afforded by the WQC), if the sediment meets either one of the following benchmarks:

- The solid phase benchmark: $\sum_i[SEM_i] < [AVS]$; in other words, if metal, measured as SEM, does not exceed AVS; or

- The interstitial water benchmark: $\sum_i([M_{i,d}]/FCV_{i,d}) < 1$; in other words, if the sum of the contributions of all six metals in the interstitial water would not be expected to cause chronic effects at the level of protection afforded by the WQC.

If the AVS or interstitial water ESBs is exceeded, there is reason to believe that the sediment might be unacceptably contaminated by these metals. Further evaluation and testing would, therefore, be necessary to assess actual toxicity and its causal relationship to the metals of concern. If data on the sediment-specific SEM, AVS, and organic carbon concentrations are available, the uncertainty bounds for $(\sum SEM\text{-}AVS)/f_{OC}$ described in the metals ESB could be used to further classify sediments as those in which metals are not likely to cause toxicity, metal toxicity predictions are uncertain, or metal toxicity is likely. For sediments in which toxicity is

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

likely or uncertain, acute and chronic tests with species that are sensitive to the metals suspected to be of concern, acute and chronic sediment toxicity identification evaluations (TIEs), in situ community assessments, and seasonal and spatial characterizations of the SEM, AVS, and interstitial water concentrations would be appropriate (Ankley et al., 1994).

4.5.11. Soil Toxicity

Variability among soil toxicity test results is due in part to the influence of soil properties on bioavailablity of metals (e.g., pH, organic matter and CEC). See Sections 3.1, 3.4.6, and 3.2, covering environmental chemistry bioavailability, terrestrial bioavailability, terrestrial exposure issues. Additionally, incorporation of sparingly soluble substances, such as many environmental forms of metals, into the soil matrix is difficult, and acclimation/adaptation of test organisms can further complicate test results. Use of soluble metal salts with the addition of organism to the test matrix immediately after mixing is not representative of most environmental situations, where aging and other physical/chemical processes affect metal speciation and uptake. Furthermore, testing of soil microbial function is particularly problematic because the test substance is added to soils with the microbial population already in place and that contain background amounts of metals.

4.5.11.1. *Application*

Modifications to standard toxicity bioassays for plants and soil organisms to account for properties of metals were discussed in an expert workshop and subsequently provided in Fairbrother et al. (2002). These modifications include directions on type of soil matrices to use, mixing and aging of metals into the soil, and cautions about acclimation of test organisms. Future studies conducted specifically for development of toxicity endpoint values for metals can follow these suggested protocols and circumvent many of the past problems.

There is, however, a large body of literature on toxicity of metals to soil organisms that has already been developed, although often the objectives were to understand processes rather than to develop defensible toxicity thresholds. The challenge, therefore, lies in how to use these data, taking into account the test-to-test variability in soil chemistry parameters, and 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. Ideally, an aquatic BLM could be extended to terrestrial setting to account for

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

differences in bioavailability due to environmental chemistry, particularly for plants and soft-bodied soil invertebrates. Studies have been initiated to develop what has been referred to as a *terrestrial BLM*, or tBLM. The conceptual approach to development of a tBLM is very much the same as for the variations of the BLMs that have been developed for aquatic settings (Allen, 2002). Although not currently developed to the point of being of practical use, experimental testing and model development programs are fully underway in the hope of providing a tool that will be of great practical utility in the relatively near future.

Another approach to addressing soil variability in soil toxicity tests is to normalize test results by dividing the LC50 by percent organic matter (van Gestal, 1992). This approach is based on observed correlations between the LC50 of copper to earthworms and soil organic matter content. Most recently, CEC has been shown to be the most important factor modifying zinc bioavailability in soils for both invertebrates and plants, and it will presumably show a similar relationship with other cationic metals (Smolders, 2003 presentation in DC; based on work by C. Janssen, Univ. Ghent). Therefore, effect responses in different soil types can be normalized on the basis of relative CEC. It should be remembered that CEC is a function, at least in part, of soil pH. Therefore, normalization can be done only among soils of similar pH ranges. However, comparison of field data with laboratory toxicity response information is best done through measuring metals in soil pore water from field assessments and comparing such data to spiked laboratory soils.

Several studies of plants and invertebrates have suggested that consideration of aging may result in significant overestimates of field effects using data laboratory studies (e.g., Smit and Van Gestel, 1998). Estimates of effects of aging (see Section 4.1.7.2., Environmental Chemistry for an aging discussion) range from 3 to 8-fold differences between laboratory and field results.

Because most soil properties are correlated to some degree, isolating individual soil parameters and relating them to soil biota toxicity is difficult. Treating the soil like a black box and using sequential extraction techniques has been useful in determining what fraction of the metals are in a labile form (Kabata-Pendias and Pendis, 2000). However, some scientists have questioned the usefulness of this process (Morgan and Morgan, 1988).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.11.2. *Limitations*

Only two methods have been proposed in the literature for normalizing toxicity data across soils to account for differences in bioavailability: adjusting of endpoint values by percent organic matter in the soil or as a function of organic matter plus clay content. Both methods fail to incorporate either pH or cationic exchange capacity, both of which are of critical importance in determining bioavailability. Aging of metals in soils also is not included in these approaches. Furthermore, the data sets used to generate the relationships were not sufficiently robust to make generalizations possible across all soils and all organisms. The development of a tBLM shows promise as a method that will overcome these limitations; however, it likely will not be completed for at least 2 years after the publication of this Framework.

The use of a tissue residue approach has been suggested as another method to address soil chemistry and metal toxicity issues, suggesting that a metal concentration must reach a threshold value in the organism or at the target site before effects begin to occur (McCarthy and Mackay, 1993; Lanno and McCarty, 1997). For essential elements in plants, deficiency/sufficiency concentrations in foliage have been developed. However, the relationship between toxicity and tissue residues is complex and varies depending on tissue type (roots vs. shoots), plant species, and metal. Little information is available for soil invertebrates, so relationships between tissue concentration and toxic response cannot yet be developed. Therefore, this approach, although conceptually sound, requires significant research before critical tissue levels can be established.

For plants, a large proportion of the toxicity literature was developed in support of understanding potential toxicity and metal uptake from biosolids (e.g., sewage sludge). It is difficult to determine single-species, single-metal thresholds from this database for several reasons. First, biosolids tend to contain a mixture of metals, so any response observed cannot be attributed to a single metal and should account for potential antagonism or synergies that might occur. Second, biosolids are, by their nature, high in organic matter, which significantly affects bioavailability of the metals. Until a robust method is developed to adjust toxicity endpoints for the influence of organic matter (and other bioavailability factors), it will remain difficult to apply such results to unamended soils. The additional organic matter also provides excess nutrients to the plants, which further confounds possible metal effects. The guidance for development of Ecological Soil Screening Levels or EcoSSL (U.S. EPA, 2003c) can be used to judge the applicability of literature studies to plant or soil invertebrate toxicity threshold determinations.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

4.5.12. Food Chain (Wildlife) Toxicity

Toxicity in wildlife from metals exposures is generally poorly understood and is rarely quantified in field settings. A few notable exceptions are those mechanisms described in avian waterfowl exposure to selenium (Adams et al., 2003), exposure of waterfowl to lead-contaminated sediments (Beyer et al., 1998; Blus et al., 1991; Henny et al., 2000), and white-tailed ptarmigan exposure to cadmium in vegetation (Larison et.al., 2000). Most metals express multiorgan toxicity, resulting in a general decrease in overall vigor, as opposed to well-defined mechanisms of action documented from organic xenobiotics such as pesticides. Typically, toxicological data used to assess the risk of many metals to wildlife are derived from laboratory species such as rats or mice or domestic livestock species (e.g., cattle and chickens) exposed to soluble metal salts. Extrapolating the results of such tests to evaluate toxicity to wildlife is necessary because of the paucity of data on the toxicity of metals to these receptors. However, extrapolation of results should be approached with caution due to the large amount of uncertainty that could be introduced into the risk assessment process (Suter, 1993).

Laboratory and domestic species may be more or less sensitive to chemicals than is the selected receptor. Toxicological responses among species vary because of many physiological factors that influence the toxicokinetics (absorption, distribution, and elimination) and toxicodynamics (relative potency) of metals after exposure has occured. For example, differences in gut physiology, renal excretion rates, and egg production influence the toxicokinetics of metals. The ability of some species to more rapidly produce protective proteins such as metallothionein after exposure to metals are toxicodymamic features leading to interspecific extrapolation uncertainty. For example, mammal studies should not be extrapolated to birds, and extrapolation of data from rats (simple, monogastric digestive physiology) to ruminants introduces more uncertainty than does extrapolation from rats to canids, and so on. In the case of metals, 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.

4.5.12.1. *Application*

Methods for extrapolating metal effects data among species are not unique to metals risk assessment, with the exception of understanding different requirements for essential elements. Some of the methods for extrapolating effects data among species include body weight normalization (Sample and Arenal.,1999), distribution-based approaches (Van Straalen, 2001),

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

or the use of uncertainty factors (e.g., Calabrese and Baldwin, 1994). All of these approaches suffer from a lack of an underlying physiological basis quantifying toxicokinetic and toxicodynamic responses among species. A review of potential extrapolation methodologies can be found in Kapustka et al. (2004).

Currently, the best sources of information on metal toxicity thresholds are NAS/NRC (1980; 1994), McDowell (2003), and the documentation supporting development of EcoSSLs values (U.S. EPA, 2003c). The EcoSSL document also includes a general approach for screening studies for acceptability for use in derivation of toxicity thresholds for risk assessments that can be used for deriving site-specific TRVs for the most applicable endpoints. These endpoints should then be extrapolated to species with similar physiology, particularly of the digestive system, due to the predominance of the dietary exposure pathway (e.g., cow data can be applied to wild bovids such as bison and possibly to other ruminants such as deer or elk). Uncertainty factors can be carefully applied if there is concern for extrapolation of data to species in a different taxonomic category (e.g., genus, family or class). General summaries for some metals are available in Beyer et al. (1996) and Fairbrother et al. (1996).

4.5.12.2. *Limitations*

Information on toxicity of metals to wildlife under field conditions is severely limited, focusing on only a few species and a few metals. Deriving TRVs for metals in wildlife is problematic because the administered form of metal is typically not found in most applied settings. For example, lead has one of the largest databases for laboratory exposures but has been limited by the form of the metal studied. Until recently, almost all field studies were conducted in support of toxic effects of lead shot (i.e., pure elemental lead), whereas almost all laboratory studies have administered lead to test subjects as lead acetate. These extreme forms of lead relative bioavailability make extrapolations to dietary exposures difficult for this substance. The best approach in this case is the use of critical tissue residues, because liver lead levels indicative of lead poisoning are well established (Beyer et al., 1996). Selenium is another example where tissue-based toxicity thresholds (in this case, in the avian egg) may be most appropriate (e.g., Adams et al., 2003).

Cross-species extrapolations should be conducted with some knowledge of animal physiology and specific responses to metals. Digestive physiology is the most important distinction, because most metal exposures in wildlife are by the dietary route. However, other specific organismal responses should be understood as well. For example, sheep are much more

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

sensitive to copper than are other ruminants because of the particular nature of their gut flora (NAS/NRC, 1980). Therefore, extrapolation of sheep data to other ruminants would be highly overconservative. On the other hand, pigs are extremely tolerant to copper, possibly due to low gut uptake rates (NAS/NRC, 1980), so extrapolations of such data to other monogastric animals would not be protective.

Interactions of metals (see Section 3.3. Human Health) also should be taken into account when analyzing metal toxicity data for wildlife. As noted above, values that may be protective for a particular metal within a certain animal may not be so if other metals are present or deficient (or vice versa). Therefore, dietary studies should be examined to understand the presence of other metals and to ascertain the sufficiency of essential elements. Application of single-metal thresholds to field situations, whether in a site-specific context or on a national scale, should make provision for adjustment to account for interactive effects.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

5. METALS RESEARCH NEEDS

The field of metals risk assessment has been advancing rapidly for more than 5 years, as reflected in the large amount of information described in this document. However, significant uncertainties and gaps remain that require additional research if accurate assessments are to be conducted. This chapter briefly reviews major, ongoing research programs within and outside EPA and provides a list of recommendations for future research endeavors. This chapter is not intended to outline a research strategy for metals risk assessment. Rather, it discusses the current direction of metals-related research conducted by EPA, external institutions, and academia as it relates to uncertainties and gaps in metals risk science.

5.1. U.S. EPA RESEARCH

EPA has devoted significant resources to researching metals-related topics, and a variety of metals-related endeavors are planned and under way in an ongoing effort to better understand the behavior and effects of metals in humans and the environment and to advance the field of metals risk assessment. Specific summaries of metals-related research at EPA are available for viewing on the Agency's Science Inventory, a searchable catalog of EPA research available at http://cfpub.epa.gov/si. In addition, EPA's Office of Research and Development (ORD) has a multiyear planning effort to guide the direction of its research program. The purpose of the multiyear plans (MYPs) is to provide a framework that integrates research across ORD's laboratories and centers. The MYP for contaminated sediments describes a number of projects planned and under way that involve current topics and research needs. The most recently available MYPs are available for review at http://www.epa.gov/osp/myp.htm. Examples of planned and ongoing Agency research and assessment projects involving metals topics include the following:

- Ecological effects of selenium on soil invertebrates to support the development of soil-screening limits for selenium (fiscal year [FY] 2004).

- Ecological assessment of the risks associated with ground water contamination and exposures (FY 2005).

- Characterization and assessment of the impact of metals speciation on ecological receptors (FY 2006).

- Evaluation of stabilization of metals in sediments (FY 2007).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Evaluation of perturbation on metals speciation and ecological receptors (FY 2008).

5.2. EXTERNAL RESEARCH

The Metals in the Environment Research Network (MITE-RN) is a network of collaborating institutions with participants from academia, government, and industry, formed in 1998 with the aim of developing a better understanding of sources of metals in the environment, how metals move and transform within the environment, and how they can affect ecosystems and human health (www.mite-rn.org). MITE-RN has been funded at approximately $7 million for the period 1999–2004 and has been refunded for the next 5 years (2005–2010). Funding consists of contributions from the Mining Association of Canada; National Sciences and Engineering Research Canada; the Ontario Power Generation Inc.; "in-kind" contributions from Environment Canada, Fisheries and Oceans Canada, and Natural Resources Canada; and funding support from the International Lead Zinc Research Organization, International Copper Association, and Nickel Producer's Environmental Research Organization. MITE-RN has published many research articles covering all of the topics discussed in the framework (www.mite-rn.org/files/mite-rn_pubs.pdf). The most recent compilation of papers may be found in Human and Ecological Risk Assessment, vol. 9 (4).

Several universities have established multidisciplinary research centers for metals. For example, under a grant from the National Institutes of Environmental Health Sciences (NIEHS), Harvard University has established the Metals Research Core, which promotes innovative research among investigators who are studying the environmental fate and health effects of exposure to metals and related fields with emphasis on potential gene-metal, metal nutrient, and metal-metal interactions (www.hsph.harvard.edu/niehs/metals.html). The Agency funds a multi-institutional Center for Study of Metals in the Environment, coordinated out of the University of Delaware and including Colorado School of Mines, Manhattan College, McMaster University, Ohio State University, Oklahoma State University, University of Wyoming, and University of Missouri at Rolla (www.ce.udel.edu/CSME/Index.html). The Center for Air Toxic Metals® (CATM®) at the University of North Dakota Energy and Environmental Research Center (EERC), established in 1992 by the U.S. EPA's Office of Environmental Engineering and Technology, develops information on trace elements that can be used to develop pollution prevention strategies (www.eerc.und.nodak.edu/catm/). Dartmouth's Toxic Metals Research Center is an interdisciplinary group that studies how arsenic and other metals affect human health and the environment (http://www.dartmouth.edu/~toxmetal/). The Agency also funds the

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Hazardous Substance Research Centers (HSRCs), which address metals-linked topics, such as mining, contaminated sediments, and ground water contamination. Web sites for HSRCs may be accessed at:

http://www.engr.colostate.edu/hsrc/new.html
http://www.hsrc.org/hsrc/html/ssw/newsletter/sswnews.html
http://wrhsrc.oregonstate.edu/publications/index.htm

The metals industry also sponsors research conducted at both public and private institutions worldwide. Sponsors include the International Lead Zinc Research Organization (www.ilzro.org), the International Copper Association (www.ica.org), the Nickel Producer's Environmental Research Organization (www.nipera.org), the International Zinc Association (www.iza.org), Eurometeaux, the International Cobalt Association, and the International Council on Mining and Metals (www.icmm.com).

5.3. SPECIFIC RECOMMENDATIONS

The information provided here is a summary of research recommendations provided in the metals issue papers (http://cfpub2.epa.gov/ncea/raf/recordisplay.cfm?deid=59052) and additional comments provided by reviewers of this framework.

5.3.1. Environmental Chemistry

In general, environmental chemistry of metals research could benefit from:

- The development of more routine chemical-species-specific analytical methods.
- The development of extraction techniques that have general utility in assessing bioavailability and/or mobility.
- The validation of geochemical and chemical-specific environmental fate and transport models.
- Additional research on metal mobility and how to apply the Diffuse Layer (DL) adsorption model to metal behavior in soils and sediments using estimated values.
- Increased understanding of metal chemistry in sediments, including the redox behavior metals.
- Research to understand the chemical and physical forms of metals in the primary media of exposure.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Improved reliability of aging predictions.

5.3.2. Bioaccumulation and Bioavailability

5.3.2.1. *Aquatic*

- Evaluation of the bioaccumulation of metals bound to colloidal material in ambient water.

- More thorough evaluation of the efflux rates of metals from different animals, including specific tissues, following bioaccumulation from the dissolved phase and from the dietary pathway.

- Evaluation of metal bioaccumulation in aquatic bacteria, which may influence the fluxes of certain metals in aquatic systems and which may introduce metals into bacteria-based food chains.

- A more detailed knowledge base is required on the basic physiology and ecology of organisms that are used or at least have the potential to serve as bioindicator organisms. Furthermore, monitoring programs could focus on key biomarkers of exposure and effects and would be wise to develop an algorithm to calculate an integrated stress index.

- New approaches to evaluate the bioaccumulation of metals from waters in which there are numerous contaminants (such as would be found in most contaminated harbors or rivers) to assess synergistic and antagonistic effects.

- With regard to the BCF/BAF model, development of additional guidance should be directed at reducing uncertainty and consideration should be given to:
  - Articulating the limitations of the BCF/BAF approach.
  - When the BCF/BAF approach is or is not applicable.
  - How the BCF/BAF approach could be modified.
  - What alternative measures and criteria could be used to better account for metal bioaccumulation in relation to toxicity potential.

5.3.2.2. *Terrestrial Soil Organisms*

- Development and validation of empirical and mechanistic models linking soil physicochemical characteristics, metal speciation, and toxic effects and bioaccumulation in soil invertebrates (e.g., Biotic Ligand Model (BLM) for soil organisms).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Development and validation of kinetics models describing metal bioaccumulation in soil invertebrates.

- Basic research on the physiology of metal metabolism in various groups of soil invertebrates; evaluation of the relevance of soil pore water or diet in exposure and partitioning of metals in soil invertebrates.

- Identification of the risks for predators associated with the consumption of soil invertebrates containing metals; evaluation of the risk to predators of consuming metal partitioned to different fractions in soil invertebrates (e.g., storage granules versus metallothionein).

- Development of metal-specific biomarkers capable of quantitatively detecting magnitude and species of metal exposure.

5.3.3. Exposure

Research on exposure issues is best defined with regard to the particular receptors; hence, this section is divided into discussions of exposure research for human, terrestrial, and aquatic organisms.

5.3.3.1. *Human Health Receptors*

- Research to improve sampling, measurement approaches, and exposure models.

- Data on rates of soil and surface dust ingestion, including estimates of central tendencies, both short-term and long-term, inter- and intraindividual variability (e.g., within-age and across ages), and relative contributions of surface dust and soil.

- Information about the types and frequencies of activities that place children in contact with contaminated soils, dusts, or surfaces (e.g., hand-to-mouth behavior, rates of contact with surfaces).

- Methods to predict concentrations in surface dust, a primary medium of contact, from measurements made in surface soil samples, surface dust wipe samples, and surface dust vacuum samples.

- Better estimates of dietary intakes of metals.

- Information on the contribution of locally harvested foods to metal intakes (e.g., uptake of metals from soil, intakes of home-grown or home-harvested foods).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

5.3.3.2. *Aquatic Receptors*

- Define the best ways of expressing exposure concentration.

- Accommodate differences in exposure durations.

- Combining exposure concentrations when exposure involves metal mixtures.

- Assess the relative merits of different methods used to express exposure concentrations in sediments and suspended solids.

- Compare the simple extrapolation methods to richer survival or time-to-event models is essential.

5.3.3.3. *Terrestrial Receptors*

- Conduct further work to define or reduce the associated uncertainty of using generalized wildlife exposure models.

- Develop laboratory test data for soil systems that better reflect the actual forms of metals in field soil.

- Develop data for terrestrial receptors on the joint effect of metals in mixtures.

5.3.4. Human Health Effects

- Research should be conducted concerning the potential interactions between essential metals and nonessential metals and between nonessential metals (i.e., metal mixtures).

- Research should be conducted concerning the applicability of toxicokinetic and toxicodynamic models for risk assessment for metals and inorganic metal compounds. Consideration should be given to differences in models for essential and nonessential metals, for low versus high dose exposures, for multipathway exposures, and for mixtures of metals with multiple modes of action.

- Research is needed on methods to assess mixed (or multiple) exposures, including occupational exposures.

- There should be further research and development regarding the use of biomarkers, especially genomic, transcriptomic, and proteomic methodologies as endpoints and their relationship to frank effects on human health endpoints used in risk assessment.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- Speciation of metals in tissues of target organs should be determined. Research should be conducted on mechanisms of toxicity, including carcinogenicity, and on whether carcinogenicity of specific metals is a threshold or nonthreshold event.

- Research is needed to meet the needs of sensitive individuals on the basis of genetic and developmental factors.

- Research should be conducted to determine the potential essential or beneficial effects of metals and inorganic metal compounds (especially as these effects impact low-dose extrapolation).

5.3.5. Characterization of Ecological Effects

Because of significant differences in ecology, physiology, and toxicology of aquatic and terrestrial organisms, research recommendations are provided separately for each group.

5.3.5.1. *Toxicological Research Needs*

- **Test matrix.** Perform tests under conditions that are representative of environmentally relevant exposure conditions to form a basis for development of methods to extrapolate from laboratory to field conditions, and from site to site in the field in situations where the water-, sediment-, or soil-quality characteristics are quite variable.

- **Model development.** Develop descriptive statistical models that establish the boundaries for which the results are applicable. Develop predictive speciation and uptake models, such as the Free Ion Activity Model (FIAM) or Terrestrial Biotic Ligand Model (tBLM).

- **Test design.** Conducting a concerted effort to generate reasonably complete concentration-response surfaces for metals in major soils representative of larger areas of the continent would be very useful. Test designs should be based on regression models and strive to depict the range of responses from relatively low concentrations to relatively high concentrations.

- **Measurement endpoints.** Multiple endpoints should be scored over the course of the in-life portion of tests. Data on growth parameters, overall healthiness of test organisms, and behavioral and reproductive endpoints should be explored. Such data could be useful in developing descriptive statistical models, including multiple regressions and clustering analyses. In addition, such data could be used to calibrate predictive models that attempt to relate effects across exposure periods.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

- **Interspecies extrapolation.** Studies designed to develop interspecies extrapolation models, especially for terrestrial organisms, are necessary.

- **Interactions among metals.** Research to understand interactive effects, for both acute and chronic exposures, is necessary. Methods for representing the joint effects of metal mixtures on the organism, in the context of the BLM, have been proposed, but these methods have not been implemented or tested to date.

5.3.5.2. *Ecological Research Needs*

- **Extrapolations from laboratory to field.** Studies documenting the correspondence or lack of correspondence between simple laboratory toxicity tests and field assessments are necessary. In situations where laboratory and field results are inconsistent, research is necessary to identify factors that contribute to these differences.

- **Indirect effects of metals and species interactions.** Studies of the effects of metals on species interactions and their ecological significance are needed.

- **Acclimation and adaptation to metals.** Additional research is necessary to understand the cost of tolerance and adaptation to metals and the potential consequences with regard to exposure to multiple stressors.

5.3.6. Unit World Model for Metals

Recognizing the continuing need to overcome limitations in understanding and, therefore, adequately predicting metal behavior in the environment, it has been proposed that use of a suite of evolving computational modeling tools could provide the basis for metals assessments, particularly for hazard ranking and screening-level risk assessments. The model would be run for a generic environment (the "Unit World"), giving output in the form of substance-specific loadings that would result in accumulations in target compartments that equal specified toxicity thresholds (e.g., LC_{50}, EC_{25}), known as the "critical load." It is anticipated that such outputs could be used for both classification and priority ranking as well as for regional (or national) screening assessments. For screening assessments, an attempt is made to describe how the substance will behave in the environment, to which media it will partition (e.g., air, soil, or water), how long it will persist, in which media it will primarily degrade, and ultimately, what mass input will result in media that will cause a toxic effect. These assessments introduce an illustrative or hypothetical release into a hypothetical, evaluative region of interest. The model yields calculated masses, concentrations, and rates of transport and transformation that are

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

entirely fictitious. Features that do not depend on the quantity of chemical or specific environmental characteristics, such as environmental persistence, relative importance of degradation and transport pathways, and relative concentrations among media, can be deduced. It should be noted that the decision point for whether an assessment of toxicity is required is derived through an evaluation of environmental fate processes.

This approach also could be used to conduct a risk assessment in which real emission rates are introduced into a model construct of a real environment in an attempt to calculate real masses and concentrations. These predicted environmental concentrations (PECs) can be compared with measured values to evaluate the performance of the model and with concentrations below which adverse toxicological effects are not expected to occur (e.g., PNECs). This comparison results in an assessment of the risk of an adverse effect at the predicted concentration.

A "critical load" is defined as the mass per unit time of a substance that, when introduced into the environment, results in accumulations in environmental media that reach specified toxicity thresholds. Key inputs are toxicity data (acute or chronic thresholds) for individual environmental compartments and the physical and chemical properties of the substance. Fate models may be envisioned as being run in reverse to back-calculate the loading that results in achieving the specified toxicity concentration. Processes that affect fate and potential exposure of organisms, such as intercompartmental transfer, complexation, and adsorption and precipitation reactions, are included. Since many of the fate processes that affect metal ions and organic compounds are similar, a common modeling framework may be envisioned for organic substances and metals, with processes (e.g., biodegradation) turned on or off as required, depending on the nature of the substance.

Unit World Model

The **Unit World Model** calculates the mass loading needed to achieve the critical load of metal in each environmental compartment (soil, sediment, water). A ***critical load*** is the amount of substance in the environment that results in specified toxicity thresholds.

The Unit World approach uses models derived from previous modeling efforts for metals for aquatic systems (e.g., Di Toro, 2001; Bhavsar et al., submitted). The aim is to produce a model that is similar but that includes the processes that are necessary to describe the behavior of metals in both aquatic and terrestrial environments simultaneously. The model is not intended to represent a specific location but, rather, a representative setting that is typical of the class of environments being evaluated. It also is not intended to be a complete description of metal fate and transport. Rather, it focuses on the primary processes that affect the toxicity and long-term

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

fate of metals. It is designed to be used for evaluative purposes, not for detailed site-specific evaluation.

The model framework, presented in Figure 5-1, is composed of an aquatic and terrestrial sector. The model is formulated as a series of mass balance equations that are formulated assuming that the rates of adsorption and desorption are fast relative to the other processes (i.e., the local equilibrium assumption). By contrast, the kinetics of metal sulfide precipitation and dissolution are formulated as kinetic processes. The concentrations and characteristics of the necessary water column and particulate partitioning phases will be established to represent the "unit worlds" to be used in the evaluation.

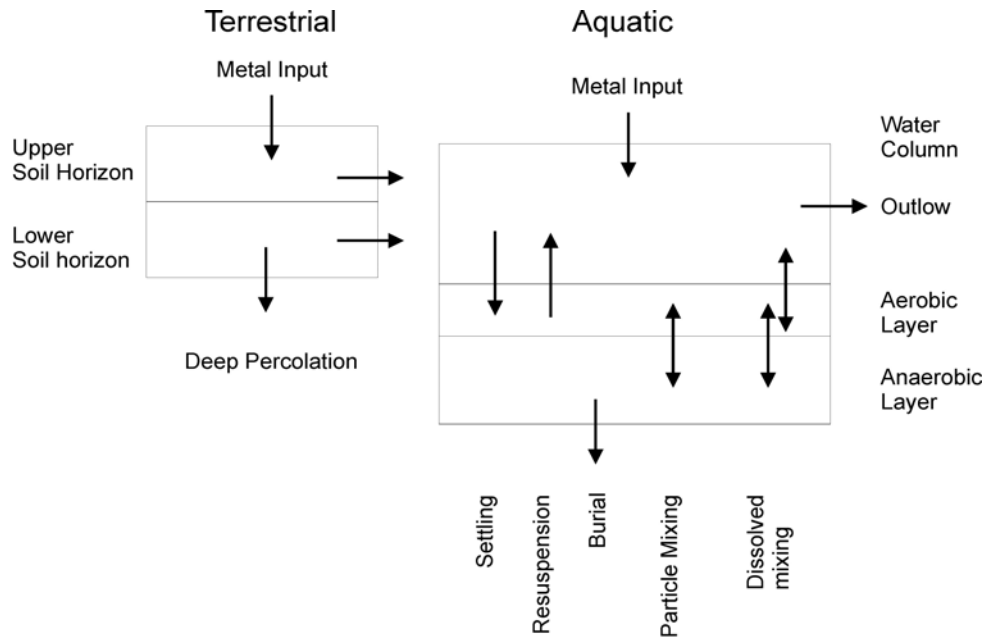

Figure 5-1. Schematic representation of the Unit World Model for Metals.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Partitioning in the water column and aerobic sediment layer is computed using WHAM6/SCAMP (Tipping, 1998; Lofts and Tipping, 1998). These models have been calibrated with laboratory data and have parameters for many of the metals that are of interest. Some field testing has also been performed with reasonable results (Bryan et al., 2002; Lofts and Tipping, 1998). The aqueous phase speciation includes dissolved organic carbon (DOC) complexation. The particulate partitioning phases are organic carbon; the oxides of Al, Si, Mn, and Fe; and a mineral cation exchanger. The concentrations of these particulate phases are specified externally as part of the input parameters. SCAMP assumes that the partitioning to these phases is additive. The importance of metal sulfide precipitation in the anaerobic layer and subsequent oxidation in the aerobic layer is well known, and models of these phenomena have been developed (e.g., Di Toro et al., 1996; Boudreau, 1991).

The soil model comprises two soil horizons, containing solids and solution. The upper horizon receives the metal of interest in soluble form. The soil solution flows from the upper horizon to the lower or directly to a surface water. Soil solution from the lower horizon flows to the surface water or is lost, together with dissolved metal and metal bound to suspended particulate matter (SPM), to deep percolation. The physical and chemical conditions are specified for each horizon; the upper horizon has a higher organic matter content than the lower. The processes governing metals in soils include solution speciation (described with WHAM6) and solid-solution partitioning (described using K_d values, characterized by multiple regression equations with pH and soil organic matter (Sauvé et al., 2000, 1998), and take into account competition for dissolved organic matter binding sites by Al and Fe(III) species (Tipping et al., 2002), particle aging (to be characterized for different metals on the basis of experimental information, taking account of soil pH), and the input flux of background metals from weathering. The value of F_{in} (moles m^{-2} a^{-1}) that is sought from the model corresponds to the Critical Load.

There are very few key processes that most significantly influence the outcome of the model (i.e., the critical load). These are the input terms of ecotoxicity and bioaccumulation, the speciation and partitioning reactions between water, sediment, and soil that determine both the fate—the compartments where the metal finally resides—and the bioavailability. Additionally, the transfer of metals into nonbioavailable forms has a significant impact on the critical load. In this model, these transfer processes are aging reactions in soils and acid-volatile sulfide (AVS)-binding of the metal. The approach assumes that the soluble metal form is introduced to the air compartment and is distributed appropriately to the soil and water compartments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Calculation of the fraction of soluble metal relative to the parent compound, or "transfer" factor, is done separately.

The Unit World Model approach is based on well-established principles governing the environmental behavior of metals. However, at present, the proposed approach should be considered as a conceptual framework embodying components that are at different stages of development and evaluation. It will therefore be necessary to undertake a series of well-integrated activities to move forward from the conceptual stage to a fully implemented and accepted evaluative method that is capable of tracing the significant fate and transport processes of a wide range of metals and predicting both the concentration and speciation at the exposure point with a sufficient degree of accuracy to reflect the objectives of the assessment (classification, ranking, or screening-level risk assessment).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

6. GLOSSARY OF TERMS

Absolute Bioavailability (or ABA): Conventionally expressed as the fraction of the externally administered amount of a metal substance that is absorbed and reaches the systemic circulation or central compartment of the receptor.

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

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

Additivity: When the effect of the combination is estimated by the sum of the exposure levels or the effects of the individual components.

Adsorption: Adsorption is the adhesion of molecules of gas, liquid, or dissolved solids to a surface.

Antagonism: When the effect of the combination is less than that suggested by the component toxic effects.

Background: The amount of metals occurring in soils, water, or air as a result of anthropogenic and natural processes.

Bioaccessibility: The portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (e.g., fate, transport, bioaccumulation) is termed the environmentally available fraction. Also referred to as ***Environmental Availability.***

Bioaccumulation: The net accumulation of a metal in tissue of interest or the whole organisms that results from exposure from all environmental sources, including air, water, solid phases (i.e., soil, sediment), and diet, and representing a steady-state balance of losses from tissue and the body.

Bioaccumulation Factor (or BAF): The ratio of the metal concentration in an organism to that in the surrounding medium at steady state. Metal accumulation in organisms is derived from all routes of exposure.

Bioconcentration Factor (or BCF): The ratio of metal concentration in an aquatic organism to the metal concentration in water at steady state. Metal accumulation in aquatic organisms is derived from water only.

Bioavailability of Metals: The extent to which bioaccessible metals adsorb onto or absorb into

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

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.

Biomagnification: The tendency of a chemical to accumulate to higher concentrations at higher levels in the trophic system through dietary accumulation.

Biomarker: Biochemical, physiological, and histological changes in organisms that can be used to estimate either exposure to chemicals or the effects of exposure to chemicals.

Biomonitoring: Use of living organisms as "sensors" in environmental quality surveillance to detect changes in environmental conditions that might threaten living organisms in the environment.

Cation Exchange Capacity (CEC): A measure of the soil's ability to adsorb or release cations, which is proportional to the number of available, negatively charges sites. The CEC is one of the important parameters in controlling the potential bioavailability of metals in soils.

Community: An assemblage of populations of different species within a specified location in space and time.

Conceptual model: A conceptual model in problem formulation is a written description and visual representation of predicted relationships between ecological entities and the stressors to which they may be exposed.

Delft 3D model: Software package that simulates two- and three-dimensional flow, waves, water quality, ecology, sediment transport, and bottom morphology.

Donald J. O'Connor model: Algorithms for inclusion in the Simplified Lake and Stream Analysis [SLSA] model.

Dose: The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The potential dose is the amount ingested, inhaled, or applied to the skin. The applied dose is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The absorbed dose is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes. Internal dose is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction by any particular organ or cell is termed the delivered dose for that organ or

Dose-response Curve: A graphical representation of the quantitative relationship between

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

administered, applied, or internal dose of a chemical or agent, and a specific biological response to that chemical or

***Dose-Response Relationship*:** The relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

EC_{50}: A statistically or graphically estimated concentration that is expected to cause one or more specified effects in 50% of a group of organisms under specified conditions (1996). (Pertains to ecological assessments)

Ecosystem: All the living (e.g., plants, animals, and humans) and nonliving (rocks, sediments,soil,water,andair)material interacting within a specified location in time and space.

Endpoint: A measured response of a receptor to a stressor. An endpoint can be measured in a toxicity test or in a field survey.

Environmental Availability: See ***Bioaccessibility.***

Essential Metals: Trace metals present in all healthy tissue of humans, whereby their withdrawal from the body induces physiological, biochemical, and structural abnormalities and their addition either reverses or prevents these abnormalities.

***Exposure*:** Contact of a pollutant with the outer boundary of an organism; exposure is quantified as the concentration of the agent in the medium over time.

Exposure Pathway: The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site.

Exposure Route: The mechanism for which a chemical or physical agent comes in contact with a person (e.g., by ingestion, inhalation, dermal contact).

Fugacity: Tendency for a metal to transfer from one medium to another.

Ground Water: Water in a saturated zone or stratum beneath the surface or land or water.

HST3D model: A 3-Dimensional ground water flow, heat and solute transport model.

HYDRAQL model: Computer-based speciation model.

Hydrophilic: Denoting the property of attracting or associating with water molecules; characteristic of polar or charged molecules.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Hydrophobic: With regard to a molecule or side group, tending to dissolve readily in organic solvents, but not in water, resisting wetting, not containing polar groups or sub-groups.

Indirect Effects: Changes in a resource that are due to a series of cause-effect relationships rather than to direct exposure to a contaminant or other stressor. As a consequence of potential direct effects of metals on organisms (e.g., mortality, reduced fecundity), other organisms in the community can be indirectly affected (e.g., reduced prey items, predators).

Inhibition: When one substance does not have a toxic effect on a certain organ system, but when added to a toxic chemical, it makes the latter less toxic.

Integrated Risk Information System (IRIS): IRIS is an electronic database that contains EPA's latest descriptive and quantitative regulatory information about chemical constituents. Files on chemicals maintained in IRIS contain information related to both noncarcinogenic and carcinogenic health effects.

LC_{50}: A statistically or graphically estimated concentration that is expected to be lethal to 50% of a group of organisms under specified conditions

Margin of Exposure: The ratio of the critical NOAEL to the expected human exposure level.

***Mechanism of Action*:** The complete sequence of biological events that must occur to produce a toxic effect.

Metal and Metalloid: An element that acts as a cation in chemical reactions, forms a base with the hydroxyl radical, and can replace the hydrogen of an acid to form a salt. Antimony, arsenic, molybdenum, selenium, and vanadium generally occur as oxyanions in waters and soils, and not as cations. These elements are sometimes described as ***metalloids***.

MIKE21 model: Modeling tool for rivers, estuaries, and coastal waters for two-dimensional free-surface flows.

MINTEQ model: Computer-based speciation model for modeling metal partitioning in discharge; the model usually must be run in connection with another fate and transport model.

MINEQL model: Computer-based speciation model.

MINTEQA2 model: An equilibrium speciation model that can be used to calculate the equilibrium composition of dilute aqueous solutions in the laboratory or in natural aqueous systems (updates MINTEQ)**.**

Mode of Action: A less-detailed description of the mechanism of action in which some, but not all, of the sequence of biological events leading to a toxic effect is known.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

NICA model: Non-Ideal Competitive Absorption model. Computer program for studies of metals in soil moisture.

Nonthreshold Effect: An effect for which it is assumed that there is no dose, no matter how low, for which the probability of an individual's responding is zero.

Organometallics: Compounds that have a metal/metalloid-carbon bond.

Physiologically-Based Pharmacokinetic (PBPK) Model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution between target organs and tissues, metabolism, and excretion.

PHREEQC model: Speciation and reaction path calculations for freshwaters and brines.

Pollution-Induced Community Tolerance (or PICT): A tool to assess effects of pollutants on ecological communities by comparing responses of communities collected from polluted and reference sites to contaminant exposures under controlled conditions. An increase in community tolerance at a polluted site that results from the elimination of sensitive species is considered evidence that this restructuring was caused by the pollutant.

Receptors: Organisms, populations, or ecosystems that are exposed to a contaminant or other stressor.

Recommended Dietary Allowance (or RDA): The dietary level of intake of essential nutrients considered to be adequate to meet the known nutritional

REDEQL2 model: Chemical reaction model; computer programs [REDEQL and MINEQL series] to calculate chemical equilibrium in complex systems, including natural waters and manmade chemical systems.

Reference Site: A relatively uncontaminated site used for comparison to contaminated sites in environmental monitoring studies, often incorrectly referred to as a control.

RESRAD model: Family of computer risk codes developed to calculate site-specific RESidual RADioactive material guidelines as well as radiation dose and excess lifetime cancer risk to a chronically exposed on-site resident.

Reference Concentration (or RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Reference Dose (or RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

Regression Analysis: Analysis of the functional relationship between two variables; the independent variable is described on the X axis and the dependent variable is described on the Y axis (i.e. the change in Y is a function of a change in X).

***Relative Absorption Factor (or RAF)*:** Similar to the RBA, the RAF more specifically refers to the fraction or percentage of a metal that is absorbed across a biological membrane. The RAF is one of the more common measures of uptake of metals into the body from environmental exposure media.

***Relative Bioavailability (or RBA)*:** The ratio (fraction or percentage) of the amount of a metal substance of interest that is adsorbed or absorbed under defined conditions (e.g., metal salt type, specified vehicle or matrix, differing test doses, different physiological states of the receptor) as compared to a reference metal substance tested under standard conditions.

Risk: The expected frequency or probability of undesirable effects resulting from exposure to known or expected stressors.

Risk Assessment: Qualitative or quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence or release of hazardous substances, pollutants or contaminants.

Risk Characterization: A phase of risk assessment that integrates the results of the exposure and effects analyses to evaluate the likelihood of adverse effects associated with exposure to the stressor. The ecological significance of the adverse effects is discussed, including consideration of the types and magnitudes of the effects, their spatial and temporal patterns, and the likelihood of recovery.

Secondary Effect: An effect where the stressor acts on supporting components of the ecosystem, which in turn have an effect on the ecological component of interest (synonymous with indirect effects; compare with definition for primary effect).

Sediment: Particulate material lying below water.

Simultaneously extracted metals (SEM): Divalent metals, commonly cadmium, copper, lead, mercury, nickel, and zinc, that form less soluble sulfides than do iron or manganese and are solubilized during the acidification step (0.5m HCl for 1 hour) used in the determination of acid volatile sulfides in sediments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Speciation: Refers to the distribution of an element among defined chemical species, which are the specific form of an element defined as to isotopic composition, electronic or oxidation state, and/or complex or molecular structure.

Stressor: Any physical, chemical, biological entity that can induce an adverse

Synergism: When the effect of the combination is greater than that suggested by the component toxic effects.

***Susceptibility*:** Increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human subpopulation (e.g. life stage, demographic feature, or genetic characteristic).

Surface Water: Surface water is all water naturally open to the atmosphere, such as rivers, lakes, reservoirs, streams, and seas.

***Susceptible Subgroups*:** May refer to life stages, for example, children or the elderly, or to other segments of the population, for example, asthmatics or the immune-compromised, but are likely to be somewhat chemical-specific and may not be consistently defined in all cases.

***Threshold Effect*:** An effect for which there is some dose below which the probability of an individual's responding is zero.

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

Toxicity: Deleterious or adverse biological effects elicited by a chemical, physical, or biological agent.

Toxicodynamics: The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (also called pharmacodynamics).

Toxicokinetics: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals (also called pharmacokinetics).

Trophic Levels: A functional classification of taxa within a community that is based on feeding relationships (e.g., aquatic and terrestrial green plants make up the first trophic level and herbivores make up the second).

WATEQ4F model: Program model for calculating speciation of major, trace, and redox elements in natural waters.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

7. REFERENCES

Abernathy, CO; Cantilli, R; Du, JT. (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. 81–113.

Adams, WJ. (2000) Hazard identification for metals and metal compounds: an alternative to the U.S. EPA strategy for identifying hazards associated with metals and metal substances. Presentation at the expert workshop: state of the science regarding PBT concepts and metals and metal compounds. U.S. EPA, EPRI, ICA, ILZRO, NiPERA and ICME. January 19. Arlington, VA.

Adams, SM; Crumby, WD; Greeley, MS; et al. (1992) Relationships between physiological and fish population responses in a contaminated stream. Environ Toxicol Chem 11:1549–1557.

Adams, WJ; Conard, B; Ethier, G; et al. (2000) The challenges of hazard identification and classification of insoluble metals and metal substances for the aquatic environment. Hum Ecol Risk Assess 6:1019–1038.

Adams, WA; Brix, KV; Edwards, M; et al. (2003) Analysis of field and laboratory data to derive selenium toxicity thresholds for birds. Environ Toxicol Chem 22(9):2020–2029.

AIHA (American Industrial Hygiene Association). (2003) The occupational environment: its evaluation, control, and management. 2nd Edition. Ed. Salvatore Dinardi. Fairfax, VA; AIHA Press, American Industrial Hygiene Association: pp 37-38, 356.

Allen, HE. (2002) Bioavailability of metals in terrestrial ecosystems: Importance of partitioning for bioavailability to invertebrates, microbes and plants. ISBN 1-880611-46-5. Society of Environmental Toxicology and Chemistry. 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, USEPA ERL ORD, Athens, GA. EPA/600/3-91/021.

Alloway, BJ. (1995) Metals in soils, 2nd ed. New York: Blackie Academic & Professional, Chapman & Hall.

Ambrose, RB; Wool, TA; Martin, JL. (1993) The water quality analysis simulation program, WASP5. Version 5.10 . Part A: Model documentation. U.S. Environmental Protection Agency, Athens, GA .

Ambrose, T.M., M. Al-Lozi, and M.G. Scott. (2000) Bone lead concentrations assessed by in vivo x-ray fluorescence. Clin. Chem. 46:1171-1178.

Andersen, M.E, H.J. Clewell, M.L. Gargas, F.A. Smith, and R.H. Reitz. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87:185-205.

Andersen, ME. (1995) Development of physiologically based pharmacokinetic and physiologically based pharmacodynamic model for applications in toxicology and risk assessment. Toxicol Lett 79:35

Ankley, GT; Phipps, GL; Leonard, EN; et al. (1991) Acid-volatile sulfide as a factor mediating cadmium and nickel bioavailability in contaminated sediments. Environ Toxicol Chem 10:1299–1307.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Ankley, GT; Mattson, V; Leonard, E; et al. (1993) Predicting the acute toxicity of copper in freshwater sediments: evaluation of the role of acid volatile sulfide. Environ Toxicol Chem 12:312–320.

Ankley, GT; Phipps, GL; Leonard, EN; et al. (1991) Acid-volatile sulfide as a factor mediating cadmium and nickel bioavailability in contaminated sediments. Environ Toxicol Chem 10:1299–1307.

Ankley, GT; Di Toro, DM; Hansen, DJ; et al. (1996) Technical basis and proposal for deriving sediment quality criteria for metals. Environ Toxicol Chem 15:2056–2066.

Antonovics, J; Bradshaw, AD; Turner, RG. (1971) Metal tolerance in plants. Adv Ecol Res 7:1–85.

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.

Archer, D; Emerson, S; Reimers, C. (1989) Dissolution of calcite in deep-sea sediments: pH and oxygen microelectrode results. Geochim Cosmochim Acta 53:2831–2845.

Arnold, PT; Kapustka, LA. (1993) Comparative uptake kinetics and transport of cadmium and phosphate in *Phleum pratense-Glomus deserticolum* associations. Environ Toxicol Chem 12:177–186.

Arnold, M.L., F.E. McNeill, and D.R. Chettle. (1999) The feasibility of measuring manganese concentrations in human liver using neutron activation analysis. Neurotoxicology 20:407-412.

ATSDR (Agency for Toxic Substance and Disease Registry). (1995) Multiple lead and cadmium exposure study with biological markers incorporated. Atlanta, GA.

ATSDR (1999a) Toxicological profile for Lead. Atlanta, GA

ATSDR (1999b) Toxicological profile for Mercury. Atlanta, GA.

ATSDR (2003) Toxicological profile for Nickel, Draft for Public Comment, Atlanta, GA.

ATSDR (2004) Evaluation of the toxicology of chemical mixtures commonly found at hazardous waste sites. Draft. Atlanta, GA.

AWWA (American Water Works Association). (1999) Water Quality and Treatment. A Handbook of Community Water Supplies. 5th Edition. 1233 pp. ISBN 0-07-001659-3.

Azar, A; Snee, RD; Habibi, K. (1975) An epidemiologic approach to community air lead exposure using personal air samplers. In: Griffin, TB; Knelson, JH, eds. Lead. Stuttgart: Georg Thieme Pub; pp. 254–290.

Azenha, M; Vasconcelos, MT; Cabral, JPS. (1995) Organic ligands reduce copper toxicity in Pseudomonas syringae. Environ Toxicol Chem 14:369–373.

Baas-Becking, LGM; Kaplan, IR; Moore, D. (1960) Limits of the natural environment in terms of pH and oxidation-reduction potentials. J. Geol. 68:243-284.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Babukutty, Y; Chacko, J. (1995) Chemical partitioning and bioavailability of lead and nickel in an estuarine system. Environ Toxicol Chem 14:427–434.

Bailey, RG. (1998) Ecoregions: the ecosystem geography of the oceans and continents. New York: Springer.

Bailey, MR; Roy, M. (1994) Clearance of particles from the respiratory tract. Annals of the ICRP (Publication No. 66) 24(1–3):301–413.

Ball, JW; Runkel, RL; Nordstrom, DK. (1999) Transport modeling of reactive and nonreactive constituents from Summittville, Colorado: Preliminary results from the application of the OTIS/OTEQ model to the Whitman Fork/Alamosa River System. In: Proc. Technical Meeting, Charleston, SC, Mar. 8-12, 1999. Vol. 1 of 3. Contamination from hard-rock mining. U.S. Geological Survey Water Resources Investigations Report 99-4018A.

Ballatori, N. (2002) Transport of toxic metals by molecular mimicry. Environ Health Perspect 110(Suppl. 5):689–694.

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

Barbour, MT; Plafkin, JL; Bradley, BP; et al. (1992) Evaluation of EPA's rapid bioassessment benthic metrics: metric redundancy and variability among reference stream sites. Environ Toxicol Chem 11:437–449.

Barltrop, D. (1966) The prevalence of pica. Am J Dis Child 112:116–123.

Barltrop, D; Meek, F. (1979) Effect of particle size on lead absorption from the gut. Arch Environ Health 34:280–285.

Barnes RM. (1990) Childhood soil ingestion: how much dirt do kids eat? Anal Chem 62:1023–1033.

Basta, NT; Pantone, DJ; Tabatabai, MA. (1993) Path analysis of heavy metal adsorption by soil. Agron J 85:1054–1057.

Beck, BD; Mattuck; RL; Bowers, TS; et al. (2001) The development of a stochastic physiologically-based pharmacokinetic model for lead. Sci Total Environ 274:15–19.

Beckett, PHT. (1989) The use of extractants in studies on trace metals in soil, sewage sludges, and sludge-treated soils. Adv Soil Sci 9:143–176.

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. 32:33-38.

Benjamin, MM; Leckie, JO. (1981) Competitive adsorption of Cd, Cu, Zn and Pb on amorphous iron hydroxides. J. Colloid Interface Sci. 83:410-419.

Berding, V; Schwartz, S; Matthies, M. (1999) Visualisation of the complexities of EUSES. Environ Sci Pollut Res 6:37–43.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Berglund, M., A. Askesson, B. Nermell, and M. Vahter. (1994) Intestinal absorption of dietary cadmium in women depends on body stores and fiber intake. Environ. Health Perspect. 102:1058-1065.

Berry, WJ; Hansen, DJ; Mahony, JD; et al. (1996) Predicting the toxicity of metal-spiked laboratory sediments using acid-volatile sulfide and interstitial water normalizations. Environ Toxicol Chem 15:2067–2079.

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

Beyer, WN; Audet, DJ;, Morton, A; et al. (1998) Lead exposure of waterfowl ingesting Coeur d'Alene River Basin sediments. J Environ Qual 27:1533–1538.

Biesinger, KE; Christensen, GM; Fiandt, JT. (1986) Effects of metal salt mixtures on *Daphnia magna* reproduction. Ecotoxicol Environ Saf 11:9–14.

Binder, S; Sokal, D;Maugham, G. (1986) Estimating soil ingestion: the use of tracer elements in estimating the amount of soil ingestion by young children. Arch Environ Health 41:341–345.

Bingham, FT; Sposito, G; Strong, JE. (1986) The effect of sulfate on the availability of cadmium. Soil Sci 141:172–177.

Bjerregaard, P., S. Topçuoglu, N.S. Fisher and S.W. Fowler. (1985) Accumulation and retention of ^{237}Pu and ^{241}Am in the mussel Mytilus edulis. Mar. Ecol. Prog. Ser. 21:99-111.

Blanck, H; Wangberg, SA; Molander, S. (1988) Pollution-induced community tolerance: a new ecotoxicological tool. In: Cairns, J, Jr; Pratt, JR,eds. Functional testing of aquatic biota for estimating hazards of chemicals. ASTM STP 998. American Society for Testing and Materials, Philadelphia, PA; pp. 219–230.

Blumberg, AF; Mellor, GL. (1987) A description of a three-dimensional coastal ocean circulation model. In: Heaps, N, ed. Three-dimensional coastal ocean models. American Geophysical Union, Washington, DC.

Blus, LJ; Henny, CJ; Hoffman, DJ; et al. (1991) Lead toxicosis in tundra swans near a mining and smelting complex in northern Idaho. Arch Environ Contam Toxic 21:549–555.

Bodek, IB; Lyman, WJ; Reehl, WF; Rosenblatt, DH, eds. (1988) Environmental inorganic chemistry: Properties, processes, and estimation methods. SETAC Spec. Publ. Ser. New York: Pergamon Press.
Bohn, HL; McNeal, BL; O'Connor, GA. (1985) Soil chemistry, 2nd ed. New York: John Wiley & Sons.

Bogumil, R; Faller, Pl; Binz, PA; Vasak, M; Charnock, JM; and Garner, CD. (1998) Structural characterization of Cu(I) and Zn(II) sites in neuronal-growth-inhibitory factor by extended X-ray absorption fine structure (EXAS). Eur.J. Biochem. 255:172-177.

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. 13:53-60.

Bossuyt, BT; Janssen, CR. (2002). Influence of bioavailability on acclimation of Daphnia magna to copper. Mededelingen Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen 67(4). 2002. 133-136.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Bowers, TS; Mattuck, RL. (2001) Further comparisons of empirical and epidemiological data with predictions of the integrated exposure uptake biokinetic model for lead in children. Hum Ecol Risk Assess 7(6):1699–1713.

Bowers, TS; Beck, BD; Karam, HS. (1994) Assessing the relationship between environmental lead concentrations and adult blood lead levels. Risk Anal 14(2):183–189.

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.

Brady JA, Gemmiti-Nunn D, Polan AK, Mitchell D, Weil R, Vianna NJ. (1980) The relationship of dental practice characteristics to blood mercury levels. NY State Dental J 46:420-424.

Brix, KV; DeForest, DK. (2000) Critical review of the use of bioconcentration factors for hazard classification of metals and metal compounds. Parametrix, Inc., Kirkland, WA.

Brooks, RR. (1972) Geobotany and biogeochemistry in mineral exploration. New York: Harper & Row.

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, PL; Markich, SJ. (2000) Evaluation of the free ion activity model of metal-organism interaction: extension of the conceptual model. Aquat Toxicol 51:177–194.

Brown, GE, Jr; Foster, AL; Ostergren, JD. (1999a) Mineral surfaces and bioavailability of heavy metals: a molecular-scale perspective. Proc Natl Acad Sci 96:3388–95.

Brown, SL; Chaney, RL; Berti, W. (1999b) Field test of amendments to reduce the in situ availability of soil lead. In: Wenzel, WW; Adriano, DC; Alloway, B; et al., eds. Abstracts of the 5th international conference on biogeochemistry of trace elements. International Society for Trace Element Research. July 11–15, Vienna, Austria.

Brown, SL; Henry, CL; Compton, H; et al. (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 17–20, 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* 13:1971-1983.

Bullock, O.R. (2000) Current methods and research strategies for modeling atmospheric mercury. Fuel Processing Technology 65-66:459-471; EPA/600/J-00/261.

Bullock, O.R. (2000) 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, 2000.

Bullock, O.R., and Brehme, K.A. (2002) Atmospheric mercury simulation using the CMAQ model: formulation description and analysis of wet deposition results. Atmospheric Environment 36 (13):2135-2146; EPA/600/J-03/227.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Burgess, RM; Scott, KJ. (1992) The significance of in-place contaminated marine sediments on the water column: processes and effects. In Burton GA, Jr., ed. Sediment toxicity assessment. Boca Raton, FL: Lewis Publishing; pp 129-154.

Cabana, G; Tremblay, A; Kalff, J; et al. (1994) Pelagic food chain structure in Ontario lakes: a determinant of mercury levels in lake trout (*Salvelinus namaycush*). Can J Fish Aquat Sci 51:381–389.

Calabrese, EJ; Baldwin, LA. (1994) A toxicological basis to derive a generic interspecies uncertainty factor. Environ Health Perspect 102:14–17.

Calabrese, EJ; Stanek, EJ. (1993) Soil pica:nNot a rare event. J Environ Sci Health (Part A) 28:373–384.

Calabrese, EJ; Barnes, R; Stanek, EJ, III; et al. (1989) How much soil do young children ingest: an epidemiologic study. Regul Toxicol Pharmacol 10:123–137.

Calabrese, EJ; Stanek, EJ; Gilbert, CE; et al. (1990) Preliminary adult soil ingestion estimates: results of a pilot study. Regul Toxicol Pharmacol 12:88–95.

Calabrese, EJ; Stanek, EJ, III; Pekow, P; et al. (1997) Soil ingestion estimates for children residing on a Superfund site. Ecotoxicol Environ Safety 36:258–268.

Calamari, D; Alabaster, JS. (1980) An approach to theoretical models in evaluating the effects of mixtures of toxicants in the aquatic environment. Chemosphere 9:533–538.

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. 45-102.

Campbell, PGC; Hansen, HJ; Dubreuil, B; et al. (1992) Geochemistry of Quebec North Shore salmon rivers during snowmelt: organic acid pulse and aluminum mobilization. Can J Fish Aquat Sci 49:1938–1952.

Campbell, PGC; Hontela, A; Rasmussen, JB; Giguère, A; Gravel, A; Kraemer, L; Kovesces, J; Lacroix, A; Levesque, H; Sherwood, G. (2003) Differentiating between direct (physiological) and food-chain mediated (bioenergetic) effects on fish in metal-impacted lakes. Human Ecol Risk Assess 9: 847-866.

Capar, S.G. and W.C. Cunningham. (2000) Element and radionuclide concentrations in food: FDA Total Diet Study 1991-1996. J. AOAC International. 83:157-177.

Carbanaro, R. (1999). Modeling metal sulfide fluxes from sediments. MS thesis. Department of Environmental Engineering. Manhattan College, Riverdale, NY.

Carignan, R; Tessier, A. (1985). Zinc deposition in acid lakes: the role of diffusion. Science, 228, 1524-1526.

Carlisle, JC; Wade, MJ. (1992) Predicting blood lead concentrations from environmental concentrations. Regul Toxicol Pharmacol 16:280–289.

Carlisle, J., J. Christopher, B. Davis, K. Klein, B. Renzi, and M. Wade. (2000) Updated version of the California

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

EPA lead risk assessment spreadsheet model for predicting blood lead in children and adults. Available at: http://www.dtsc.ca.gov/docs/sppt/herd/ledspred.html

Carlson, AR; Phipps, GL; Mattson, VR; et al. (1991) The role of acid-volatile sulfide in determining cadmium bioavailability and toxicity in freshwater sediments. Environ Toxicol Chem 10:1309–1319.

Casas, AM; Crecelius, EA. (1994) Relationship between acid volatile sulfide and the toxicity of zinc, lead and copper in marine-sediments. *Environ Toxicol Chem* 13:529-536.

Cataldo, DA; Wildung, RE. (1978) Soil and plant factors influencing the accumulation of heavy metals by plants. Environ Health Perspect 27:149–159.

Cederberg, GA; Street, RTL; Leckie,JO. (1985) A groundwater mass transport and equilibrium chemistry model for multicomponent systems. Water Resour. Res. 21:1095-1104.

CDC (Center for Disease Control and Prevention) (1991). Preventing lead poisoning in young children. Atlanta, GA, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.

CDC (2003) National Report on Human Exposure to Environmental Chemicals: Second Report) available at www.cdc.gov/exposurereport

Chaney, RL. (1980) Health risks associated with toxic metals in municipal sludge. In: Bitton, G., B.L. Damron, G.T. Edds, and J.M. Davidson, eds. Sludge—Health risks of land application. AnnArbor, MI: Ann Arbor Sci. Publ. Inc., pp. 59-83.

Chaney, RL; Mielke, HW; Sterrett, SW. (1988) Speciation, mobility and bioavailability of soil lead. In: Davis, BE; Wixon, BG, eds. Lead in soil: issues and guidelines. Northwood: Science Reviews; pp. 104-129.

Chaney, RL; Ryan, JA. (1993) Heavy metals and toxic organic pollutants in MSW-composts: Research results on phytoavailability, bioavailability, etc. In: Hoitink, A.J. and H.M. Keener, eds. Science and engineering of composting: Design, environmental, microbiological and utilization aspects. Columbus, OH: Ohio State University, pp. 451-506.

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

Chaney, RL; Mielke, HW; Sterrett, SW. (1988) Speciation, mobility and bioavailability of soil lead. In: Davis, BE; Wixon, BG, eds. Lead in soil: issues and guidelines. Northwood: Science Reviews; pp. 104-129.

Chaney, RL; Brown, SL; Angle, JS; et al. (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. 34:4931-4935.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Chapman, GA. (1987) Establishing sediment criteria for chemicals: regulatory perspective. In: Dickson, KL; Maki, AW; Brungs, WA, eds. Fate and effects of sediment-bound chemicals in aquatic systems.New York: Pergamon Press; pp 355-376.

Chapman, PM; Wang, F. Undated. Issues in ecological risk assessments of inorganic metals and metalloids. Available at: http://www.uoguelph.ca/cntc/files/era-metals.pdf.

Chapman, PM; Wang, F. (2000) Issues in ecological risk assessment of inorganic metals and metalloids. Hum Ecol Risk Assess 6(6):965–988.

Chapman, PM; Dias, GM (2003) [DRAFT] Topic: Assessing Atmospheric Metals Deposition. ORD Order No. 3W-0748-NASX.

Chapman, PM; Wang, F; Janssen, CR; et al. (2003) Conducting ecological risk assessments of inorganic metals and metalloids: current status. Human Ecol Risk Assess 9:641–697.

Charlatchka, R; Cambier, P; Bourgeois, S. (1997) Mobilization of trace metals in contaminated soils under anaerobic conditions. In: Prost, R, ed. Contaminated soils. Proceedings of the 3rd international conference on biogeochemistry trace elements. May 15–19, Paris, France.

Chen, CY; Folt, CL. Bioaccumulation and diminution of arsenic and lead in a freshwater food web. Environmental Science & Technology. 34(18):3878-3884.

Chen, Z; Mayer, LM. (1998) Mechanisms of Cu solubilization during deposit feeding. Environ Sci Technol 32:770775.

Cherian, MD; Goyer, RA. (1995) Part Three, Chapter 9, Section A, In: Berthon, G. ed. Handbook of metal-ligand interactions in biological fluids, Vol. 1. New York: Marcel Dekker, Inc., pp. 648-654.

Chiodo LM; Jacobson, SW; Jacobson, JL. (2004). Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol. 26(3):359-71.

Choudhury, H; Harvey, T; Thayer, WC; et al. (2001) Urinary cadmium elimination as a biomarker of exposure for evaluating a cadmium dietary exposure-biokinetics model. J Toxicol Environ Health 63:101–130.

Cia, L; Tsiapalis, G; Cherian, MG. (1998) Protective role of zinc metallothionein on DNA damage in vitro by ferric nitriloacaetate (Fe-NTA) and ferric salts. Chem-Biol Interact 115:141–151.

Clark TP, Chieffo C, Huhn JC, Nimz EL, Wang C, Boy MG. (2003) The steady-state pharmacokinetics and bioequivalence of carprofen administered orally and subcutaneously in dogs. J Vet Pharmacol Ther. 2003 Jun;26(3):187-92.

Clarke, R.H. (1995) ICRP recommendations applicable to the mining and minerals processing industries and to natural sources. International Commission on Radiological Protection. Health Phys. 69:454-60.

Clarkson, TW. (1986) Effects—general principles underlying the toxic action of metals. In: Friberg, L; Nordberg, GF; Vouk, V. eds. Handbook on the toxicology of metals, 2nd ed., Vol. 1. Amsterdam: Elsevier, pp. 85-127.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Clarkson, TW. (1993) Molecular and ionic mimicry of toxic metals. Ann Rev Pharmacol Toxicol 32:545–571.

Clausing, P; Brunekreef, B; van Wijen, JH. (1987) A method for estimating soil ingestion by children. Int Arch Occup Environ Health 59:73–82.

Clayton, CA; Pellizzari, ED; Whitmore, R; et al. (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 Epidem 9:381–392.

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 Epidem 12:29–43.

Clements, WH; Cherry, DS; Van Hassel, JH. (1992) Assessment of the impact of heavy metals on benthic communities at the Clinch River (Virginia): evaluation of an index of community sensitivity. Can J Fish Aquat Sci 49:1686–1694.

Clewell, HJ. (1995) The application of physiologically based pharmacokinetic modeling in human health risk assessment of hazardous substances. Toxicol Lett 79:207–217.

Cohen, J.T., B.D. Beck, T.S. Bowers, R.L. Bornschein, and E.J. Calabrese. (1998) An arsenic exposure model: Probabilistic validation using empirical data. Hum. Ecol. Risk Assess. 4(2):341-377.

Conder, JM; Seals, LD; Lanno, RP. (2002) Method for determining toxicologically relevant cadmium residues in the earthworm *Eisenia fetida*. Chemosphere 49:1–7.

Coombs, TL; George, SG. (1978) Mechanisms of immobilization and detoxication of metals in marine organisms. In: McLusky, DS; Berry, JA, eds. Physiology and behavior of marine organisms. Oxford: Pergamon Press; pp. 179–187.

Crecelus, EA; Hardy, JT; Bobson, CI; et al. (1982) Copper bioavailability to marine bivalves and shrimp: Relationship to cupric ion activity. Mar Environ Res 6:13–26.

Cress, WA; Throneberry, GO; Lindsey, DI..(1979) Kinetics of phosphorus absorption by mycorrhizal and nonmycorrhizal tomato roots. Plan Physiol 64:484–487.

Crist, ME; Oberhoiser, K; Schwartz, D; et al. (1988) Interactions of metals and protons with algae. Environ Sci Technol 22:755–760.

Crommentuijn, T; Doodeman, CJAM; Van der Pol, JJC; et al. (1994) Lethal body concentrations and accumulation patterns determine time-dependent toxicity of cadmium in soil arthropods. Environ Toxicol Chem 13:1781–1789.

Crommentuijn, T; Doodeman, CJAM; Van der Pol, JJC: et al. (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 5:261–271.

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. Journal of AOAC International 78: 897-909.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Dabeka RW; McKenzie, AD; Lacroix, GM; Cleroux, C; Bowe, S; Graham, RA; Conacher, HBS; Verdier, P. (1993) Survey of arsenic in total diet food composites and estimation of the dietary intake of arsenic by Canadian adults and children. Journal of AOAC International 76:14-25.

Davison, AG; Taylor, A; Darbyshire, J. (1988) Cadmium fume inhalation and emphysema. Lancet 26:663-667.

Davidson, W; Zhang, H. (1994) In situ speciation measurements of trace components in natural waters using thin-film gels. Nature 367:546–548.

Davis, S; Waller, P; Buschbom, JR; et al. (1990) Quantitative estimates of soil ingestion in normal children between the ages of 2 and 7 years: population-based estimates using aluminum, silicon, and titanium as soil tracer elements. Arch Environ Health 45:112–122.

Dawson, DC; Ballatori, N. (1995) Membrane transporters as site of action and routes of entry for toxic metals. In: Goyer, RA; Cherian, MG, eds. Toxicology of metals: biochemical aspects. New York: Springer-Verlag; pp. 53–76.

Delos, CG; Richardson, WI; DePinto, JV; et al. (1984) Technical guidance manual for performing waste load allocations: Book II. streams and rivers. U.S. Environmental Protection Agency, Office of Water, Washington, DC.

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. 36:48-54.

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. 23:1365-1375.

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 133:243-

DeVoto, E; Yokel, RA. (1994) The biological speciation and toxicokinetics of aluminum. Environ Health Perspect 102:940–51.

Diamond, ML. (1995) Application of a mass balance model to assess in-place arsenic pollution. Environ. Sci. Technol. 28(1): 29-42.

Diamond, ML; Mackay, D; et al. (1990) A model of the exchange of inorganic chemicals between water and sediments. Environ Sci Technol 24:713–722.

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.

Diamond ML; Mackay, D; Cornett, RJ; Chant, L. (1990) A model of the exchange of inorganic chemicals between water and sediments. *Environ. Sci. Tech.* 24: 713-722.

Dias, GM; Edwards, GC. (2003) Differentiating natural and anthropogenic sources of metals to the environment. Human Ecol Risk Assess 9: 699-721.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Dill, LM; Heithaus, MR; Walters, CJ. (2003) Behaviorally mediated indirect interactions in marine communities and their conservation implications. Ecology 84: 1151-1157.

Di Toro, DM. (1984) Probability model of stream quality due to runoff. J Environ Engineer ASCE 110:607–628.

Di Toro, DM. (1987) Modeling the fate of toxic chemicals in surface waters. Short course notes from 8th annual SETAC meeting. Pensacola, FL.

Di Toro, DM. (2001). Sediment flux modeling. New York: J. Wiley and Sons; pp 624.

Di Toro, DM; Fitzpatrick, JJ; Thomann, RV. (1981) Water quality analysis simulation program (WASP) and model verification program (MVP). Hrydroscience Inc. for U.S. EPA. Grosse Ile Laboratory, Grosse Ile, MI (revised in 1983).

Di Toro, DM; Mahony, JD; Hansen, DJ; et al. (1990) Toxicity of cadmium in sediments: the role of acid volatile sulfide. Environ Toxicol Chem 9:1487–1502.

Di Toro, D M; Hallden, JA; et al. (1991) Modeling ceriodaphnia toxicity in the Naugatuck River: II. copper, hardness and effluent interactions. Environ Toxicol Chem 10:261–274.

Di Toro, DM; Mahony, JD; Hansen, DJ; et al. (1992). Acid volatile sulfide predicts the acute toxicity of cadmium and nickel in sediments. Environ Toxicol Chem 26:96–101.

Di Toro, DM; Mahony, JD; Hansen, DJ; et al. (1996) A model of the oxidation of iron and cadmium sulfide in sediments. Environ Toxicol Chem 15:2168–2186.

Di Toro, DM; Hansen, DJ; McGrath, JA; et al. (1999) Predicting the toxicity of metals in sediments. In: Integrated approach to assessing the bioavailability and toxicity of metals in surface waters and sediments. Presented to the EPA Science Advisory Board, Office of Water, Office of Research and Development, Washington, DC. EPA-822-E-99-001.

Di Toro, DM; Allen, H; Bergman, H; et al. (2000) Biotic ligand model of the acute toxicity of metals: I. technical basis. Environ Toxicol Chem 20(10):2383–2396.

Di Toro, DM; Allen, HE; Bergman, HL; Meyer, JS; Paquin, PR; Santore, RC. (2001) A biotic ligand model of the acute toxicity of metals. I: Technical basis. Environ. Toxicol. Chem. 20:2383-2396.

Di Toro, DM; McGrath,JA; Hansen, DJ; Berry, WJ; Paquin, PR; Mathew, R; Wu, KB; Santore, RC. (2004) Predicting sediment metal toxicity using a sediment biotic ligand model: (I) single metals. Submitted.

Dlugaszek, M; Fiejka, MA; Graczy, A; et al. (2000) Effects of various aluminum compounds given orally to mice on Al tissue distribution and tissue concentrations of essential elements. Annu Rev Pharmacol Toxicol 86:135–139.

Domingo, JL. (1995) Reproductive and developmental toxicity of aluminum: a review. Neurotoxicol Teratol 17:515–521.

Duggan, MJ; Inskip, MJ. (1985) Childhood exposure to lead in surface dust and soil: a community health problem. Public Health Rev 13:1–54.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Duggan, MJ; Inskip, MJ; Rundle, SA; et al. (1985) Lead in playground dust and on the hands of schoolchildren. Sci Total Environ 44(1):65–80.

Dzombak, DA; Ali, MA. (1993) Hydrochemical modeling of metal fate and transport in freshwater environments. Watr Pollut Res J Can 28(1):7–50.

Dzombak, DA; Morel, FMM. (1990) Surface complexation modeling: Hydrous ferric oxide. New York: Wiley InterScience.

EC (European Commission). (1996) EUSES documentation: the European Union system for the evaluation of substances. National Institute of Public Health and the Environment (RIVM), The Netherlands.

Efroymson, RA; Sample, BE; Suter GW, II. (2001) Bioaccumulation of inorganic chemicals from soil by plants: regressions of field data. Environ. Toxicol. Chem 20:2561-2571.

Egan, SK; Tao, SS; Pennington, JA; et al. (2002) U.S. Food and Drug Administration's total diet study: intake of nutritional and toxic elements, 1991-1996. Food Addit Contam 19:103–125.

Ellis, KJ; Vartsky, D; Zanzi, I; et al. (1979) Cadmium: in vivo measurement in smokers and nonsmokers. Science 205:323–325.

Enserink, EL; Maas-Diepeveen, JL; Van Leeuwen, CJ. (1991) Combined effects of metals: an ecotoxicological evaluation. Wat Res 25:679–687.

Epstein, E. (1965) Mineral metabolism. In: Bonner, J; Varner, JE.,eds. Plant biochemistry. London: Academic Press; pp. 438–466.

Epstein, E. (1972) Mineral nutrition of plants: principles and perspectives. New York: John Wiley & Sons.

(EC Health and Consumer Protection) European Commission Health & Consumer Protection Directorate-General Directorate C – Public Health and Risk Assessment C7 – Risk Assessment Brussels, C7/GF/csteeop/WFD/280504 D(04) Opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) On "The Setting of Environmental Quality Standards for the Priority Substances included in Annex X of Directive 2000/60/EC in Accordance with Article 16 thereof " Adopted by the CSTEE during the 43rd plenary meeting of 28 May 2004

EU (European Union) (1996). Technical Guidance Document in support of commision directive 93/67/EEC on risk assessment for new notified substances and commission regulation (EC) No 1488/94 on risk assessment of existing substances. Part II. Brussles, European Union. ISBN 92-827-8012-0.

Fairbrother, A. ed. (2002) Test Methods for Hazard Determination of Metals and Sparingly Soluble Metal Compounds in Soils. SETAC Press, Pensacola, FL.

Fairbrother, A. (2003) Lines of evidence in ecological risk assessment. Human Ecol. Risk Assess. 9:1475-1491.

Fairbrother, A; Kapustka, LA. (1997) Hazard classification of inorganic substances in terrestrial systems: A discussion paper. International Council on Metals and the Environment, Ottawa, Canada.

Fairbrother, A., L. Locke, and G. L. Hoff, eds. (1996) Non-infectious diseases of wildlife. 2nd Ed. Iowa State

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

University Press, Ames, IA.

Fan, W; Wang, W-X. (2001) Sediment geochemical controls on Cd, Cr, and Zn assimilation by the clam *Ruditapes philippinarum*. Environ Toxicol Chem 20:2309–2317.

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 48:1–5.

Felmy, AR; Brown, SM; Onishi, Y; et al. (1984) MEXAMS: the metals exposure analysis modeling system. U.S. Environmental Protection Agency, Athens, GA. NTIS No. PB84 157155.

Fergusson, JE; Ryan, DE. (1984) The elemental composition of street dust from large and small urban areas related to city type, source and particle size. Sci Total Environ 34:101–116.

Field, L; Macdonald, D; et al. (2002). Predicting amphipod toxicity from sediment chemistry using logistic regression models. Environ Toxicol Chem 21(9):1993–2005.

Finney, DJ. (1947) Probit analysis: a statistical treatment of the sigmoidal response curve. Cambridge, UK: Cambridge University Press.

FIU (Florida International University), Dietary Reference Intakes (DRIs)/Recommended Dietary Allowances (RDAs) (2004) Dietary Reference Intakes for Older Adults (updated 03/19/04), compiled by the National Policy and Resource Center on Nutrition and Aging, FIU, Miami, FL.

Fisher, NS. (1986) On the reactivity of metals for marine phytoplankton. Limnol Oceangr 31:443-447.

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. 30:3232-3242.

Fleming, D.E.B., D.R. Chettle, J.G. Wetmur, R.G. Desnick, J. Robin, D. Boulay, N.S. Richard, C.L. Gordon, and C.E. Webber. (1998) Effect of the d-aminolevulinic dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ. Res. 77:49-61.

FNB (Food and Nutrition Board). (2000) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington: National Academies Press. Summary Pp 1-28.

Forstner, U. (1987) Sediment-associated contaminants: an overview of scientific basis for developing remedial options. Hydrobiologia 149:221–246.

Forstner U. (1995a) In: Biogeodynamics of Pollutants in Soils and Sediments. W Salomons, WM Stigliani (Eds). Springer, Berlin.

Forstner, U. (1995b) Land contamination by metals: Global scope and magnitude of the problem. In: Allen, H. Et al., eds. Metal speciation and contamination of soil. Boca Raton, FL: Lewis Publishers.

Fowler BA. ed. (1983) Biological and environmental effects of arsenic. New York: Elsevier Science Publishing Company.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Fowler, BA; Mahaffey, KR. (1978) Interactions among lead, cadmium and arsenic in relation to porphyrin excretion patterns. Environ Health Perspect 25:87–90.

Foulkes, E.C. 2000. Transport of toxic heavy metals across cell membranes. Proc. Soc. Exp. Biol. Med 223:234-40.

Fowler, B.A., and K.R. Mahaffey. 1978. Interactions among lead, cadmium and arsenic in relation to porphyrin excretion patterns. Environ. Health Perspect. 25:87-90.

Foy, CD; Chaney, RL; White, MC. (1978) The physiology of metal toxicity in plants. Ann Rev Plant Physiol 29:511–566.

Franke, C; Studinger, G; Berger, G; et al. (1994) The assessment of bioaccumulation. Chemosphere 29:1501–1514.

Freeman, GB; Johnson, JD; Killinger, JM; et al. (1993) Bioavailability of arsenic in soil impacted by smelter activities following oral administration in rabbits. Fund Appl Toxicol 21: 83–88.

Freeman, G.B., RA. Schoof, M.V. Ruby, A.O. Davis, J.A. Dill, S.C. Liao, C.A. Lapin, and P.D. Bergstrom. (1995) Bioavailability of arsenic in soil and house dust impacted by smelter activities following oral administration in cynomolgus monkeys. Fundam. Appl. Toxicol. 28:215-22.

Freeze, SA; Cherry, JA (1979) Groundwater. Englewood Cliffs, NJ: Prentice Hall, Inc.

Friis, L; Petersson, L; Edling, C. (1998) Reduced cadmium levels in human kidney cortex in Sweden. Environ Health Perspect 106:175–178.

George, SG. (1982) Subcellular accumulation and detoxication of metals in aquatic animals. In: Vernberg, WB; Calabrese, A; Thurberg, FP; et al., eds. Physiological mechanisms of marine pollutant toxicity. Oxford: Academic Press.

George, SG. (1990) Biochemical and cytological assessments of metal toxicity in marine animals. In: Heavy metals in the marine environment. Furness, RW; Rainbow, PS, eds. Boca Raton, FL: CRC Press; pp.123–142.

George, E; Römheld, V; Marschner, H. (1994) Contribution of Mycorrhizal Fungi to Micronutrient Uptake by Plants. IN: Manthey, J.A., D.E. Crowley, and D.G. (eds). Biochemistry of metal micronutrients in the rhizosphere Lewis Publishers, Boca Raton, FL pp.93-110.

Gerbel, T. (1998) Suppression of arsenic induced-chromosome mutagencity by antimony. Mut. Res. 412:213-218.

Gettier, SW; Martens, DC; Donohue, SI. (1985) Soybean yield response prediction from soil and tissue manganese levels. Agron J 77:63–67.

Goodrum, PE; Diamond, GL; Hassett, JM; et al. (1996) Monte Carlo modeling of childhood lead exposure: development of a probabilistic methodology for use with the U.S. EPA IEUBK Model for Lead in Children. Hum Ecol Risk Assess 2:681–708.

Gooddy, DC; Shand, P; Kinniburgh, DG; Van Riemsdijk, WH (1995) Field-based partition coefficients for trace elements in soil solutions. Eur. J. Soil Scie. 46(2):265-286.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Gorsuch, JW; Janssen, C; Lee, CM; et al. (eds). (2002) The biotic ligand model for metals: current research, future directions, regulatory implications. Comp Biochem Physiol C 133:343.

Goyer, R.A. 1995. Transplacental transfer of lead and cadmium. In: Goyer, R.A. and M.G. Cherian, eds. Toxicology of metals. New York: Springer-Verlag, pp. 1-13.

Goyer, RA; Clarkson, TM (2001) Toxic effects of metals. In: Klaassen, CD, ed. Casarett & Doull's toxicology. New York: McGraw-Hill; pp. 811–868.

Goyer, RA; Golub, M; Choudhury, H; Hughes, M; Kenyon, E; Stifelman, M. (2004) Issue paper on the human health effects of metals. September 2004. Available at: http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119.

Grandjean, P., S.S. Brown, P. Reavey, and D.S. Young. (1994) Biomarkers of chemical exposure: State of the art. Clin. Chem. 40:1360-1362.

Granick, J.L., S. Sassa, R.D. Granick, R.D. Levere, and A. Kappas. (1973) Studies in lead poisoning II: Correlation between the ration of activated to inactivated d-aminolevulinic acid dehydrates of whole blood and the blood lead level. Biochem. Med. 8:149-159.

Graziano, JH; Blum, CB; LoIacano, NJ; et al. (1996) A human in vivo model for the determination of lead bioavailability using stable isotope dilution. Environ Health Perspect 104:176–179.

Greszta, J. (1982) Correlation between the content of copper, zinc, lead and cadmium in the soil and the content of these metals in the seedlings of selected forest tree species. Frag Flor Geobot 28:(1):29–52.

Griffin, S; Goodrum, PE; Diamond, GL; et al. (1999) Application of a probabilistic risk assessment methodology to a lead smelter site. Hum Ecol Risk Assess 5:845–868.

Gulson, BL; Pounds, JG; Mushak, P; et al. (1999a) Estimation of cumulative lead releases (lead flux) from the maternal skeleton during pregnancy and lactation. J Lab Clin Med 13(6):631–640

Gulson, BL; Mahaffey, KR; Jameson, C; et al. (1999b) Impact of diet on lead in blood and urine in female adults and relevance to mobilization of lead from bone stores. Environ Health Perspect 107(44):257–263.

Gulson, BL; Mahaffey, KR; Mizon, KJ; Korsch, M; Cameron, MA, Vimpani, G. (1995) Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. J. Lab. Clin. Med. 12:703-712.

Gunderson, BL (1995) FDA total diet study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. Journal of AOAC International, 1353-1363.

Gundersen, JK; Jorgensen, EL; Larsen, E; et al. (1992) Mats of giant sulfur bacteria on deep-sea sediments due to fluctuating hydrothermal flow. Nature 360:454–455.

Guo, Z. (2002) Review of indoor emission source models. Overview Environ. Pollut 120:533-549.

Gupta, SK; Chen, KY. (1975) Partitioning of trace elements in selective chemical fractions of nearshore sediments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Environ Lett 10:129–158.

Gustafson, JP (2003) Visual MINTEQ, version 2.14; a Windows version of MINTEQA2, version 4.0. <http://www.lwr.kth.se/english/OurSoftware/Vminteq/>

Hansen, DJ; Berry, WJ; Mahony, JD; et al. (1996) Predicting the toxicity of metal contaminated field sediments using interstitial water concentrations of metals and acid volatile sulfide normalizations. Environ Toxicol Chem 15:2080–2094.

Hare, L; Carignan, R; Heurtadiaz, MA. (1994). Field-study of metal toxicity and accumulation by benthic invertebrates – implications for the acid volatile sulfide (AVS). Limnol Oceanography 39:1653-1668.

Hare, L; Tessier, A; Borgmann, U. (2003) Metal sources for freshwater invertebrates: pertinence for risk assessment. Human Ecol Risk Assess. 9: 779-793.

Hargrove, WW; Hoffman, FM. (1999) Locating and characterizing the borders between ecoregions using multivariate geographic clustering. Oak Ridge National Laboratory, TN. Available at: http://research.esd.ornl.gov/~hnw/borders/.

Hawley, JK. (1985) Assessment of health risk from exposure to contaminated soil. Risk Anal 5:289–302.

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. 249–276.

Hendriks, AJ; Heikens, A. (2001) The power of size. 2. Rate constants and equilibrium ratios for accumulation of inorganic substances related to species weight. Environ. Toxicol. and Chem. 20:1421-1437.

Henny, CJ; Blus, LJ; Hoffman, D; et al. (2000) Field evaluation of lead effects on Canada geese and mallards in the Coeur d'Alene River Basin, Idaho. Arch Environ Contam Toxicol 39:97–112.

Hertzberg, R. C., G. E. Rice, and L. K. Teuschler. 1999. Methods for health risk assessment of combustion mixtures. Pages 105-148 in S. Roberts, C. Teaf, and J. Bean, editors. Hazardous Waste Incineration: evaluating the human health and environmental risks. CRC Press, Boca Raton.

Hill, CH. (1979) The effect of dietary protein levels on mineral toxicity in chicks. J. Nutr. 109:501-507.

Hilsenhoff, WL. (1987) An improved biotic index of organic pollution. Great Lakes Entomol 20:31–39.

Hoffman, AA; Parsons, PA. (1997). Extreme environmental change and evolution. Cambridge University Press, Cambridge, UK.

Hoffmann, MR. (1981) Thermodynamic, kinetic and extrathermodynamic considerations in the development of equilibrium models for aquatic systems. Environ Sci Technol 15:345–353.

Hogan, K; Marcus, A; Smith, R; et al. (1998) Integrated exposure uptake biokinetic model for lead in children: Empirical comparisons with epidemiological data. Environ Health Perspect 106(Suppl. 6):1557–1567.

Hook, SE. (2001) Sublethal toxicity of metals to copepods. Ph.D. dissertation. State University of New York

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(SUNY) at Stony Brook.

Hostynek, JJ; Hinz,RS; Lorence, CR; Price, M; Guy, RH. (1993). Metals and the skin. Crit. Rev. Toxicol. 23:171-235.

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, Marcell Dekker Inc., New York.

Hook, S.E., and N.S. Fisher. (2001) Reproductive toxicity of metals in calanoid copepods. Mar. Biol. 138:1131-1140.

Hook, SE; Fisher, NS. (2002) Relating the reproductive toxicity of five ingested metals in calanoid copepods with sulfur affinity. Marine Environ Res 53:161–174.

Hopkin, SP. (1989) Ecophysiology of metals in terrestrial invertebrates. London: Elsevier Applied Science.

Hostynek, J.J., Hinz, R.S, Lorence, C.R, and Guy, R.H. (1998) Human Skin Penetration by Metal Compounds. In M.S. Roberts and K.A. Walters, eds. Dermal Absorption and Toxicity Assessment, Marcel Dekker, Inc., NewYork.

Hudson, RJM; Gherini, SA; Watras, CJ; et al. (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.

Huertadiaz, MA; Carignan, R; Tessier, A. (1993). Measurement of trace-metals associated with acid volatile sulfides and pyrite in organic fresh-water sediment. Environ Sci Technol 27:2367-2372.

Huheey, JE; Keiter EA; Keiter, RI. (1993) Inorganic chemistry—principles of structure and reactivity, 4th ed. New York: Harper Collins College Publishers, 964 pp.

Hunt, A; Johnson, DL; Watt, JM; et al. (1992) Characterizing the sources of particulate lead in house dust by automated scanning electron microscopy. Environ Sci Technol 26:1513–1523.

Hursh, JB; Clarkson, TW, Miles, EF, Goldsmith, LA. (1989) Percutaneous absorption of mercury vapor by man. Arch. Environ. Health 44:120-127.

HydroQual (1982) Application guide for CMA-HydroQual chemical fate models. Report No. C113 for the Chemical Manufacturers Association Aquatic Research Task Group, Washington, DC. 201pp. Mahway, NJ.

HydroQual (1997) Documentation for the probabilistic analysis program MONTE. Mahway NJ.

HydroQual (1998) A primer for ECOMSED, Version 1.3. Mahway NJ.

LTI. (1994) Dynamic toxics wasteload allocation model (DYNTOX), version 2.0 user's manual. Ann Arbor, MI..

IARC (International Agency for Research on Cancer) (2004) Inorganic and organic lead compounds. Volume 87. Available at: http://www-cie.iarc.fr/htdocs/announcements/vol87.htm

Idaho Department of Health and Welfare (2000) Coeur d'Alene River Basin environmental health assessment. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Ilyin, LA; Ivannikov, AT; Parfenov, YD; Stolyarov, VP. (1975) Strontium absorption through damaged and undamaged human skin. Health Phys 29:75-80.

Ingersoll, CG; Haverland, PS; Brunson, EL; et al. (1996) Calculation and evaluation of sediment effect concentrations for the amphipod *Hyalella azteca* and the midge *Chironomus riparius*. J Great Lakes Res 22:602–623.

Isaure, M.-P; Laboudique, A; Manceau, A; et al. (2002) Quantitative Zn speciation in a contaminated dredged sediment by µPixe, µ-SXRF, EXAFS spectroscopy and principal component analysis. Geochim Cosmochim Acta 66(9):1549–1567.

Jaffe, D., M. S. Landis, P. Weisspenzias, and E. Prestbo.. (2003) Comments on "Mercury Concentrations in Costal California Precipitation: Evidence of Local and Trans-Pacific Fluxes of Mercury to North America" By Steding and Flegal (2002). J Geophys Res-Atmos 108(D17):ACH 11-1 to ACH 11-2.

James, BR (1994) Hexavalent chromium solubility and reduction in alkaline soils enriched with chromite ore processing residue. J. Environ. Qual. 23:227-233.

James, AC; Stahlhofen, W; Rudolf, GR; et al. (1994) Deposition of inhaled particles. Annals of the ICRP (Pub. No. 66) 24(1–-3):231–299.

Janes, N; Playle, RC. (1995) Modeling silver binding to gills of rainbow trout (Oncorhynchus mykiss). Environ Toxicol Chem 14:1847–1858.

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

Janssen, CR; Heijerick, DG. (2003). Algal toxicity tests for environmental risk assessments of metals. IN: Ware, George W. [Editor,] Reviews of Environmental Contamination and Toxicology. 178 :23-52.

Jarup, L.; Berglund, M.; Elander, C.; Nordberg,G.; Vahter, M. (1998) Health effects of cadmium exposure—a review of the literature and a risk estimate. Scand. J. Work Environ. Health 24(Suppl 1):1-52.

Jeffree, RA. (1988) Patterns of accumulation of alkaline-earth metals in the tissue of the freshwater mussel *Velesunio angasi*. Archiv fuer Hydrobiologie112: 67-90.

Jing, J; Logan, T (1992) Effects of sewage sludge cadmium concentration on chemical extractability and plant uptake. J. Environ. Qual. 21:73-81.

Jones, MM; Vaughn, WK. (1978) HSAB theory and acute metal ion toxicity and detoxification processes. J Inorg Nucl Chem 40:2081–2088.

Kabata-Pendias, A. and H. Pendias (2001). Trace elements in soils and plants. Boca Raton, Fla., CRC Press.

Kagi, J.H.R., and Y. Kogima, eds. 1987. Chemistry and biochemistry of metallothionein. Boston: Birkhäuser, pp. 25-61.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Kahle, J; Zauke, G-P. (2003) Bioaccumulation of trace metals in the Antarctic amphipod *Orchomene plebs*: evaluation of toxicokinetic models. Marine Environmental Research 55:359-384.

Kamunde, C; Grosell, MH; Wood, CM. (2002) Copper metabolism in actively growing rainbow trout (Oncorhynchus mykiss): interactions between dietary and waterborne copper uptake. J Exp Biol 205(Pt 2)279–290.

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

Karunaratne, RS; Baker, JH; Barker, AV. (1986) Phosphorus uptake by mycorrhizal and nonmycorrhizal roots of soybean *Glycine max*. J Plant Nut 9:103–1314.

Kemp, PF; Swartz, RC. (1986) Acute toxicity of interstitial and particle-bound cadmium to a marine infaunal amphipod. Mar Environ Res 26:135–153.

Kheboian, C; Bauer, CF. (1987) Accuracy of selective extraction procedures for metal speciation in model aquatic sediments. Anal Chem 59:1417–1423.

Khoury, GA; Diamond, GL. (2003) Risks to children from remedial or removal activities at superfund sites: a case study of the rsr lead smelter Superfund site. J Exp Anal Environ Epidemiol. In press.

Kiffney, PM; Clements, WH. (1996) Effects of metals on stream macroinvertebrate assemblages from different altitudes. Ecol Appl 6:472–481.

Kimber I, Basketter DA. 1996. Contact Hypersensitivity to Metals. In: Chang LW Toxicology of Metals. Boca Raton: CRC Press, pp 827-834.

Kjellstrom, T., and G.F. Nordberg. 1978. A kinetic model of cadmium metabolism in the human being. Environ. Res. 16:248-269.

Klerks, PL; Levinton, JS. (1993) Evolution of resistance and changes in community composition in metal-polluted environments: a case study on foundry cove. In: Dallinger, R; Rainbow, PS, eds Ecotoxicology of metals in invertebrates. SETAC Special Publication Series. Ann Arbor, MI: Lewis Publishers; p. 223–241.

Kostial, K., D. Kello, S. Jugo, I. Rabar, and T. Maljkovic. 1978. Influence of age on metal metabolism and toxicity. Environ. Health Perspect. 25:81-86.

Kraak, MHS; Lavy, D; Schoon, H; et al. (1994) Ecotoxicity of mixtures of metals to the zebra mussel *Dreissena polymorpha*. Environ Toxicol Chem 13:109–114.

Krantzberg, C; Stokes, PM. (1988) The importance of surface adsorption and pH in metal accumulation by chironomids. Environ Toxicol Chem 7:653–670.

Krishnan, K., and M.E. Andersen. 1994. Physiologically based pharmacokinetic modeling in toxicology In: Hayes, A.W., ed. Principles and methods in toxicology, 3rd ed. New York: Raven Press, Ltd., pp. 149-188.

Landis, M. S., and R. K. Stevens. (2003) Comments on "Measurements of Atmospheric Mercury Species at a Costal Site in the Antarctic and Over the South Atlantic Ocean During Polar Summer"; Environ Sci Technol

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

37(14):3239-3240.

Langmuir, D. (1997) Aqueous environmental chemistry. Upper Saddle River, NJ: Prentice-Hall.

Langmuir, D; Chrostowsk, P; Vigneault, B Chaney, R. (2004) Issue paper on the environmental chemistry of metals. September 2004. <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>.

Langston, WJ. (1980) Arsenic in U.K. estuarine sediments and its availability to benthic organisms. J Mar Biol Assn UK 60:869–881.

Lanno, RP; LeBlanc, S; Knight, B; et al. (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. 41–53.

Laperche, V; Logan, TI; Gaddam, P; et al. (1997). Effect of apatite amendments on plant uptake of lead from contaminated soil. Environ Sci Technol 31:2745–2753.

Larison, JR; Likens, GE; Fitzpatrick, JW; Crock, JG. (2000). Cadmium toxicity among wildlife in the Colorado Rocky Mountains. Nature. 406:181-183.

Larsson, P. (1985) Contaminated sediments of lakes and oceans act as sources of chlorinated hydrocarbons for release to water and atmosphere. Nature 317:347–349.

Laurie, SH; Manthey, JA. (1994) The Chemistry and Role of Metal Ion Chelation in Plant Uptake Processes. IN: Manthey, J.A., D.E. Crowley, and D.G. (eds). Biochemistry of metal micronutrients in the rhizosphere Lewis Publishers, Boca Raton, FL pp. 165-182.

LaVelle, JM; Poppenga, RH; Thacker, BJ; et al. (1991) Bioavailability of lead in mining waste: an oral intubation study in young swine. In: Proceedings of the International Symposium on the Bioavailability and Dietary Uptake of Lead. Sci Technol Lett 3:105–111.

Lazo, JS; Kuo, SM; Woo, ES; Pitt, BR. (1998) The protein thiol metallothionein as an antioxidant and protectant against antineoplastic drugs. Chem Biol Interact. Apr 24,111-112:255-262.

Lee, B-G; Griscom, SB; Lee, JS; et al. (2000) Influences of dietary uptake and reactive sulfides on metal bioavailability from aquatic sediments. Science 287:282–284.

Leggett, RW. (1993) An age-specific kinetic model of lead metabolism in humans. Environ Health Perspect 101:598–616.

LePoire, D; Arnish, J; Gnanapragasam, ES; et al. (2000) Probabilistic modules for the RESRAD and RESRAD-build computer codes. NUREG/CR-XX ANL/EAD/TM-91. Argonne National Laboratory, Argonne, IL.

Liess, M; Champeau, O; Riddle, M; Schulz, R; Duquesne, S.(2001) Combined effects of ultraviolet-B radiation and food shortage on the sensitivity of the Antarctic amphipod *Paramoera walkeri* to copper. Environ Toxicol Chem 20: 2088-2092.

LePoire, D; Arnish, J; Gnanapragasam, ES; et al. (2000) Probabilistic modules for the RESRAD and RESRAD-

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

build computer codes. NUREG/CR-XX ANL/EAD/TM-91. Argonne National Laboratory, Argonne, IL.

Llobet, JM; Domingo, JL; Gomez, M; et al (1987) Acute toxicity studies of aluminum compounds: antidotal efficacy of several chelating agents. Ann Rev Pharmacol Toxicol 60:80–3.

Lindqvist, O (1994) Atmospheric cycling of mercury: An overview. In: Watras, CJ and Huckabee, JW, eds. Mercury pollution: Integration and synthesis. Boca Raton, FL: Lewis Publishers.

Lofts, S; Tipping, E. (1998) An assemblage model for cation binding by natural particulate matter. Geochem Cosmochim Acta 62(15):2609–2625.

Logan, TJ; Traina, SJ. (1993) Trace metals in agricultural soils. Chapter 10 in: Metals in Groundwater. Eds. Allen, H.E., E.M. Perdue, and D.S. Brown. New York: Lewis Publishers, pp. 309-347.

Long, ER; Morgan, LG. (1990) The potential for biological effects of sediment sorbed contaminants tested in the National Status and Trends Program. NOS OMA 52. Technical Memorandum. National Oceanic and Atmospheric Administration, Office of Oceanography and Marine Assessment, Seattle, WA.

Long, ER; Morgan, LG. (1991). The potential for biological effects of sediment-sorbed contaminants tested in the National Status and Trends Program. NOAA Tech. Memo. NOS OMA 52. Seattle, WA

Loux, NT; Brown, DS; Chafin, CR; Allison, JD; Hassan, SM. (1990) Modeling geochemical processes attenuating inorganic contaminant transport in the subsurface region: Adsorption on amorphous iron oxide. In: Murarka, I. and S. Cordle, eds. Proc. Envir. Res. Conf. on Groundwater Qual. and Waste Disposal. Report EPRI EN-6749. Palo Alto, CA: Electrical Power Research Inst.

Lu, Y; Allen, HE. (2002) Characterization of copper complexation with natural dissolved organic matter (DOM): link to acidic moieties of DOM and competition by Ca and Mg. Water Res 36:5083–5101.

Lumsdon, DG; Evans, LJ. (1995) Predicting chemical speciation and computer simulation. In: Ure, AM; Davidson, CM, eds. Chemical speciation in the environment. London: Blackie; pp. 86–134.

Luoma, SN. (1989) Can we determine the biological availability of sediment-bound trace elements? Hydrobiologia 176/177:379–396.

Luoma, SN; Bryan, GW. (1978) Factors controlling the availability of sediment-bound lead to the estuarine bivalve *Scrobicularia plana*. J Mar Biol Assn UK 58:793–802.

Ma, YB; Uren, NC. (1995) Application of new fractionation scheme for heavy metals in soils. Commun Soil Sc Plant Ana 26:3291–3303.

MacDonald, DD; Carr, RS; Calder, FD; et al. (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. 39:20-31.

Mackay, D. (1979) Finding fugacity feasible. Environ Sci Tech 13(10):1218.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Mackay, D. (1991) Multimedia Environmental Models. Chelsea, MI: Lewis Publishers.

Mackay, D; Paterson, S; et al. (1992). Generic models for evaluating the regional fate of chemicals. Chemosphere 24:695–717.

Maddaloni, M; et al. (1998) Meal-weighted bioavailability of soil-bourne lead in adults: use of empirical data analyzed by stable isotope dilution, and probabilistic worker exposure scenarios. Toxicologist 124:25.

Manceau, A; Lanson, B; Schlegel, ML; et al. (2000) Quantitative Zn speciation in smelter-contaminated soils by EXAFS spectroscopy. Fr Amer J Sci 300(4):289–343.

Manceau, A; Boisset, M-C; Sarret, G; et al. (1996) Direct determination of lead speciation in contaminated soils by EXAFS spectroscopy. Environ Sci Technol 30:1540–1552.

Markich, SJ; Brown, PL; Jeffree, RA; et al. (2000) Valve movement responses of *Velesunio angasi* (Bivalvia: Hyriidae) to manganese and uranium: an exception to the free ion activity model. Aquat Toxicol 51:155–175.

Markich, SJ; Brown, PL; and Jeffree, RA. (2001) Divalent metal accumulation in freshwater bivalves: an inverse relationship with metal phosphate solubility. The Science of the Total Environment 275: 27-41.

Marschner, H. (1995) Mineral nutrition of higher plants. ed. San Diego: Academic Press. 2nd Edition.

Marschner, H. (1998) Soil-root interface: biological and biochemical processes. In: Huang, PM, ed. Soil chemistry and ecosystem health. Soil Science Society of America, Madison, WI; pp. 191–232.

Martin, JL; Medine, AJ. (1998) Metal exposure and transformation assessment models: model documentation for version 3. Medine Environmental Engineering. Boulder, CO.

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. 479–608.

Masters, BA; Kelly, EJ; Quaife, CJ; Brinster, RL; and Palmiter, RD. (1994) Targeted disruption of metallothionein I and II genes increases sensitivity to cadmium. Proc. Nat. Acad. Sci. 91:584-588.

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 20:1890–1900.

McCarthy, LS; Mackay, D. (1993) Enhancing ecotoxicological modeling and assessment. Environ Sci Technol 27:1719–1728.

McCarty, K.M., D.B. Senn, M.L. Kile, Q. Quamruzzaman, M. Rahman, G. Mahiuddin, and D.C. Christian. 2004. Antimony: An unlikely confounder in the relationship between well water arsenic and health outcome in Bangladesh. Environ Health Perspect. 112:809-811.

McDowell, LR. (2003) Minerals in animal and human nutrition, 2nd ed. Amsterdam: Elsevier.

McGeer, JC; Playle, RC; Wood,CM; et al. (2000) A physiologically based biotic ligand model for predicting the acute toxicity of waterborne silver to rainbow trout in freshwaters. Environ Sci Technol 34:4199–4207.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

McGeer, JC; Brix, KV; Skeaff, JM; et al. (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)1017–1037.

McGeer, J; Henningsen, G; Lanno, R; Fisher, N; Sappington, K; Drexler, JW. (2004). Issue Paper on the Bioavailability and Bioaccumulation of Metals. September 2004. <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=86119>.

McGrath, SP. (1995) Chromium and nickel. In: Alloway, BJ, ed. Heavy metals in soils. London: Blackie Academic and Professional; pp. 152–178.

McKinney JD; Richard, A; Waller, C; Newman, MC; Gerberick, F. (2000) The practice of structure activity relationships (SAR) in toxicity. Toxicol Sci 56: 8-17.

McKone, T.E. 1987. Human exposure to volatile organic compounds in household tap water: The indoor inhalation pathway. Environ. Sci. Technol. 21:1194-1201.

McLaughlin, MJ; Smolders, E. (2001) A rationale for the metalloregion approach to risk assessments for metals in soil: a case study for effects of zinc on microbial functions in soil. Environ Toxicol Chem 20:2639–2643.

McLaughlin, MJ; Tiller, KG; Beech, TA; et al. (1994) Soil salinity causes elevated cadmium concentrations in field-grown tubers. Aust J Soil Res 35:1–17.

McLaughlin, MJ; Hamon, RE; Parker, DR; Pierzynski, GM; Smolders, E; Thornton, I; and Welp, G. (2002). Soil chemistry. *In*: Fairbrother, A., P.W. Glazebrook, J.V. Terazona, and N.M. van Straalan, eds. Test methods to determine hazards of sparingly soluble metal compounds in soils. Pensacola, FL: SETAC Press, pp. 5-16.

Medlin, EA. (1997) Master's thesis, Department of Geological Sciences, University of Colorado. 111 pp.

Menzie-Cura & Associates, Inc. and TN&A, Inc. (2000). Development of a framework to address bioavailability issues in wildlife. Submitted to Randall Wentsel, U.S. EPA, National Center for Environmental Assessment, Washington, D.C.

Mertz, W. (1981) The essential elements. Science 213:1332–1338.

Meyer, J. (2002) The utility of the terms "bioavailability" and "bioavailable fraction" for metals. Mar Environ Res 53:41–423.

Meyer, JS; Santore, RC; Bobbitt, JP; DeBrey, LD; Boese, CJ; Paquin, PR; Allen, HE; Bergman, HL; DiToro, DM. (1999) Binding of Nickel and Copper to Fish Gills Predicts Toxicity When Water Hardness Varies, But Free-ion Activity Does Not. Environ. Sci. and Technol 33: 913-916.

Meyer, JS; Boese, CJ; Collyard, SA. (2002) Whole-body accumulation of copper predicts acute toxicity to an aquatic oligochaete (*Lumbriculus variegatus*) as pH and calcium are varied. Comp. Biochem. Physiol. Part C 133:99-109.

Mills, WB; Porcella, DV; Ungs, MJ; et al. (1985) Water quality assessment: a screening procedure for toxic and conventional pollutants in surface and ground water. Part 1. EPA-600-6-85-002a.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Mitrofanov, D. (1993) Ability of non-woody forest plants to accumulate metals. Aquilo Ser Bot 31:41–45.

Morel, F. (1983) Complexation: trace metal and microorganisms. In: Principles of aquatic chemistry. New York: John Wiley & Sons; pp. 405–418.

Morgan, JE; Morgan, AJ. (1988) Calcium-lead interactions involving earthworms: part 2. The effects of accumulated lead on endogenous calcium in *Lumbricus rubellus*. Environ Pollut 55:41–54.

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 125:279-294.

Mowat, FS; Bundy, KJ. (2002) Experimental and mathematical/computational assessment of the acute toxicity of chemical mixtures from the Microtox assay. Adv Environ Res 6:547–558.

Moya, J., C. Howard-Reed, and R.L. Corsi. 1999. Volatization of chemicals from tap water to indoor air from contaminated water used for showering. Environ. Sci. Technol. 33:2321-2327.

Mulvey, M; Diamond, SA. (1991). Genetic factors and tolerance acquisition in populations exposed to metals and metalloids. Pages 301-321 in Newman, M.C., and A.W. McIntosh, editors. Metal ecotoxicology: concepts and applications. Lewis Publishers, Inc., Chelsea, Michigan.

Munthe, J (1994) The atmospheric chemistry of mercury: Kinetic studies of redox reactions. In: Mercury Pollution: Integration and Synthesis. Watras, CJ and Huckabee JW, eds. Boca Raton, FL: Lewis Publishers.

Mudroch, A; Azcue, JM; Mudroch, P. (1997) Manual of Physico-Chemical Analysis of Aquatic Sediments. Lewis Publishers, Boca Raton, Florida.

Mudroch, A; Azcue, JM; Mudroch, P. (1999) Manual of Bioassessment of Aquatic Sediment Quality. Lewis Publishers, Boca Raton, Florida.

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

NAS/NRC (1993) Measuring lead exposure in infants, children, and susceptible populations. Washington, DC: National Academy of Sciences Press.

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

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

NAS/NRC (2000) Toxicological Effects of methyl mercury. Washington, DC: National Academy of Sciences Press.

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

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

NAS/IOM (National Academy of Sciences/Institute of Medicine) (2000) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Food and Nutrition Board, Institute of Medicine, Washington, DC. ISBN 0-309-7279-4. Available at: http://www.nap.edu/catalog/10026.html.

NAS/IOM (2001) Dietary reference intakes for Vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Panel on Micronutrients, Food and Nutrition Board, Institute. Available at: http://www.nap.edu/catalog/10026.html

NAS/IOM (2003) Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification. Food and Nutrition Board, Institute of Medicine, Washington, DC.

NFESC (Naval Facilities Engineering Command) (2000a) Guide for Incorporating Bioavailability Adjustments into Human Health and Ecological Risk Assessments at U.S. Navy and Marine Corps Facilities. Part 1: Overview of Metals Bioavailability." Prepared by Battelle and Exponent.

NFESC (2000b) Guide for Incorporating Bioavailability Adjustments into Human Health and Ecological Risk Assessments at U.S. Navy and Marine Corps Facilities. Part 1: Technical Background Document for Assessing Metals Bioavailability. Prepared by Battelle and Exponent.

Newman, MC (1991) A statistical bias in the derivation of hardness-dependant metals criteria. Environ. Toxicol. Chem. 10: 1295-1297.

Newman, MC; McCloskey, JT. (1996) Predicting relative metal toxicity and interactions of divalent metal ions: microtox bioluminescence assay. Environ Toxicol Chem 15:275–281.

Newman, MC; McCloskey, JT; Tatara, CP. (1998) Using metal-ligand binding characteristics to predict metal toxicity: quantitative ion character-activity relationships (QICARs). Environ Health Perspect 106(Suppl. 6):1262–1270.

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

Ng, JC; Kratzmann, SM; Qi, L; et al. (1998) Speciation and absolute bioavailability: risk assessment of arsenic contaminated sites in a residential suburb in Canberra. Analyst 123:889–892.

Nieboer, E; Richardson, DHS. (1980) The replacement of the nondescript term "heavy metals" by a biologically and chemically significant classification of metal ions. Environ Pollut (Series B) 1:3-26.

Noorishad, JC, Carnahan, L.; Benson, LV. (1987) CHMTRNS: A temperature-dependent non-equilibrium reactive transport code. Earth Sciences Div., Lawrence Berkeley Laboratory.

Norwood, WP; Borgmann, U; Dixon, DG; et al. (2003) Effects of metal mixtures on aquatic biota: a review of observations and methods. Hum Ecol Risk Assess 9: 795–811.

Nott, JA; Nicolaidou, A. (1990). Mediterranean pollution from a ferro-nickel smelter: differential uptake of metals by some gastropods. Mar. Pollut. Bull. 21, pp. 137–143.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Nott, JA; Nicolaidou, A. (1994) Variable transfer of detoxified metals from snails to hermit crabs in marine food chains. Mar. Biol. 120:369-377.

Nriagu, JO; Pacyna JM. (1988) Quantitative assessment of worldwide contamination of air, water and soils by trace metals. Nature 333(6169):134-9.

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: 277-292.

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, FR:IARC; pp. 189–204.

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, FR:IARC; pp. 189–204.

O'Connor, DJ. (1988) Models of sorptive toxic substances in freshwater systems: III. streams and rivers. J Environ Engr 114 (3):552–574.

O'Flaherty, EJ. (1998) Physiologically based models of metal kinetics. Crit Rev Toxicol 28:271–317.

O'Flaherty, E.J. 1995. Physiologically based models for bone-seeking elements. V: Lead absorption and disposition in childhood. Toxicol. Appl. Pharmacol. 131:297-308.

O'Flaherty, E.J. 1993. Physiologically based models for bone-seeking elements. IV: Kinetics of lead disposition in humans. Toxicol. Appl. Pharmacol. 118:16-29.

OECD (Organization for Economic Cooperation and Development). (2001) Classification of metals and metal compounds. In: Guidance document on the use of the harmonized system for the classification of chemicals which are hazardous for the aquatic environment. (OECD Series on testing and assessment, Number 27). pp. 97–115. Document ENV/JM/MONO(2001)8. Paris, France.

Omernik, JM. (1986) Aquatic ecoregions of the conterminous United States. Supllement to the Annals of the Assoc of Amer Geographers 77:(1).

O'Rourke, M.K., P.K. van de Water, S. Jin, S.P. Rogan, A.D. Weiss, S.M. Gordon, D.M. Moschandreas, and M.D. Lebowitz. 1999. Evaluations of primary metals from NHEXAS Arizona: distributions and preliminary exposures. J. Exposure Anal. Environ. Epidemiol. 9:435-445.

Ott, WR. (1985) Total human exposure. Environ Sci Technol 10:880–886.

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 22:241–246.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Pabalan, RT; Turner, DR, Bertetti, FP; Prikryl, JD (1998) Uranium VI sorption onto selected mineral surfaces: Key geochemical parameters. Chap. 3. In Adsorption of metals by Geomedia. Ed. E.A. Jenne. Academic Press, New York: 99-130.

Pagenkopf, GK. (1983) Gill surface interaction model for trace-metal toxicity to fishes: Role of complexation, pH and water hardness. Environ Sci.Technol 17: 342–347

Paquin, PR; Santore, RC; Farley, KJ; Wu, KB; Mooney, K; DiToro, DM (2003) Review of metal fate, bioaccumulation and toxicity models for metals. Pensacola, FL: SETAC Press. In press.

Paquin, PR; Gorsuch, JW; Apte, S; Batley, GE; Bowles, KC; Campbell, PGC; Delos, CG; Di Toro, DM; Dwyer, RL; Galvez, F; Gensemer, RW, Goss, GG; Hogstrand, 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 133:3-35.

Paquin, PR; Zoltay, V; Winfield, RP; et al. (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 (Part C) 133:305–343.

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. Office of Water, Office of Research and Development.

Parent, L; Campbell, PGC. (1994) Aluminum bioavailability to the green alga *Chlorella pyrenoidosa* in acidified synthetic soft water. Environ Toxicol Chem 13:587–598.

Parker, DR; Pedler, JF. (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, The Netherlands: Kluwer; pp. 107–112.

Parkhurst, DL (2002) PHAST:3D reactive transport model. U.S. Geological Survey. <http://www.brr.cr.usgs.gov/projects/GWC_coupled/phast>

Parkhurst, DL, Appelo, CAJ (1999) User's Guide to PHREEQC (version 2)–A computer program for speciation, batch-reaction, one-dimensional transport, and inverse geochemical calculations. U.S. Geological Survey, Water Resources Inv. Report 99-4259.

Parkhurst, D.L., Thorstenson, D.C., and Plummer, L.N., 1980. PHREEQE– a computer program for geochemical calculations. U.S. Geological Survey Water-Resources Investigations Report 80-96, 210p.

Parkinson, A. 2001 Biotransformation of zenobiotics. In: Klaassen, C.D., ed. Casarett & Doull's toxicology. New York: McGraw-Hill, pp. 133-224.

Paulson, AJ; Balistrieri, LS (1999) Modeling removal of Cd, Cu, Pb, and Zn in acidic groundwater during neutralization by ambient surface waters and groundwaters. Environ. Sci. Technol. 33(21):3850-3856.

Paustenbach, DJ. (2000) The practice of exposure assessment: a state-of-the-art review. J Toxicol Environ Health

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

(Part B) 3:179–291.

Pearson, RG. (1973) Hard and soft acids and bases. Stroudsburg, PA: Dowden, Hutchinson & Ross.

Peijnenburg, WJGM; Posthuma, L; Zweers, PGPC; et al. (1999b) Prediction of metal bioavailability in Dutch field soils for the oligochaete *Enchytraeus crypticus*. Ecotoxicol Environ Saf 44:170–186.

Peijnenburg, WJGM; Baerselman, R; De Groot, AC; et al. (1999a) Relating environmental availability to bioavailability: soil-type dependent metal accumulation in the oligochaete *Eisenai andrei*. Ecotoxicol Environ Saf 44:294–310.

Persaud, D; Jacqumagi, R; Hayton, A. (1989) Development of provincial sediment quality guidelines. Draft Report. Water Resources Branch, Ontario Ministry of the Environment. Toronto, ON, Canada.

Phalen, RF; Oldham, MJ; Beaucage, CB; et al. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 212:368–380.

Picciano, M.F. 1996. Pregnancy and lactation. In: Ziegler, E.E. and L.J. Filer, Jr., eds. Present knowledge in nutrition, 7th ed. Washington, DC: ILSI Press, pp. 384-395.

Pickering, WF. (1986) Metal Ion Speciation – Soils and Sediments (A Review). Ore Geology Reviews 1:8 3.

Pillet, S., M. Fournier, L.N. Measures, J. Bousqsuegneau, and D.G. Cyr. 2002. Presence and regulation of metallothioneins in peripheral blood leukocytes of grey seals. Toxicol. Appl. Pharmacol 185:207-217.

Pitt, BR; Schwarz, M; Woo, ES; Yee, E; Wasserloos, K; Tran, S; Weng, W; Mannix, RJ; Watkins, SA; Tyurina, YY; Tyurin, VA; Kagan, VE; Lazo, JS. (1997) Overexpression of metallothionein decreases sensitivity of pulmonary endothelial cells to oxidant injury. Am. J. Physiol. 273:856-865.

Playle, RC; Wood, CM. (1990) Is precipitation of aluminum fast enough to explain aluminum deposition on fish gills? Can J Fish Aquat Sci 47:1558–1561.

Playle, RC; Dixon, DG; Burnison, K. (1993a) Copper and cadmium binding to fish gills: modification by dissolved organic carbon and synthetic ligands. Can J Fish Aquat Sci 50 2667–2677.

Playle, RC; Dixon, DG; Burnison, K. (1993b) Copper and cadmium binding to fish gills: estimates of metal-gill stability constants and modelling of metal accumulation. Can J Fish Aquat Sci 50:2678–2687.

Posthuma, L; Janssen, GM. (1995) Genetic variation for life-history characteristics in reference populations of *O. cincta* in relation to adaptation to metals in soils. Acta Zoologica Fennica 196:301–306.

Posthuma, L; Van Straalen, NM. (1993) Heavy-metal adaptation in terrestrial invertebrates: A review of occurrence, genetics, physiology and ecological consequences. Comparative Biochemistry and Physiology. 106C(1):11-38.

Posthuma, L; Baerselman, R; Van Veen, RPM; et al. (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 38:108–121.

Posthuma, L; Suter, GW; Traas, TP. eds. (2001). Species Sensitivity Distributions in Ecotoxicology, Lewis CRC-

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Presspublishers, Boca Raton, US.

Prosser, CL. (1986). Adaptational Biology; Molecules to Organisms. John Wiley & Sons, New York.

Rainbow, P.S. (2002) Trace metal concentrations in aquatic invertebrates: why and so what? *Environmental Pollution* **120**, 497-507.

Raskin, I.; Kumar, PBAN; Dushenkov, S; et al. (1994) Bioconcentration of heavy metals by plants. Curr Opin Biotechnol 5:285–290.

Regoli, F; Orlando, E. (1994) Bioavailability of biologically detoxified lead: Risks arising from consumption of polluted mussels. Environ. Health Perspectives, Supplement 3, 102: 335-338.

Reid, SD; McDonald, DG (1988) Effects of cadmium, copper and low pH on ion fluxes in the rainbow trout, *Salmo gairdneri*. Can J Fish Aquat Sci 45:244–253.
Reid, SD; McDonald, DG (1991) Metal binding activity of the gills of rainbow trout (*Oncorhynchus mykiss*). Can. J. Fish. Aquat. Sci. 48:1061-1068.

Reinfelder, JR; Fisher, NS; Luoma, SN; et al. (1998) Trace element trophic transfer in aquatic organisms: a critique of the kinetic model approach. Sci Total Environ 219:117–135.

Reinfelder, JR; Fisher, NS. (1991). The assimilation of elements ingested by marine copepods. Science 251:794–796.

Reuther, R. (1999) Trace metal speciation in aquatic sediments: methods, benefits, and limitations. In: Manual of Bioassessment of Aquatic Sediment Quality. Lewis Publishers, Boca Raton, Florida. Pp. 1-54.

Richardson, GM (2002) Natural sources and emissions of elements to the atmosphere. International Council on Mining and Metals. (February).

Robinson, B., K.R. Heid, T.L. Aldridge, and R.D. Glenn. 1983. 1976 Hanford americium exposure incident: Organ burden and radiation dose estimates. Health Phys. 45(4):911-921.

Rodriguez, RR; Basta, NT; Casteel, SW; et al. (1999) An in vitro gastrointestinal method to estimate bioavailable arsenic in contaminated soils and soil media. Environ Sci Technol 33:642–649.

Roesijadi, G. (1992) Metallothioneins in metal regulation and toxicity in aquatic animals. Aquat Toxicol 22:81–114.

Roy, I; Hare, L. (1999) Relative importance of water and food as Cd sources to the predatory insect Sialis vlata (Magaloptera). Can J Fish Aquat Sci 56(7):1143-1149.

Rozman, K.K. and C.D. Klaassen. 2001. Biotransformation of zenobiotics. In: Klaassen, C.D., ed. Casserett and Doull‘s toxicology. New York: McGraw-Hill, pp.107-132.

Ruby, MV; Davis, A; Link, TE; et al. (1993) Development of an in vitro screening test to evaluate the in vivo bioaccessibility of ingested mine-waste lead. Environ.Sci Technol 27:2870–2877.

Ruby, MV; Davis, A; Schoof, R; et al. (1996) Estimation of lead and arsenic bioavailability using a physiologically

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

based extraction test. Environ Sci Technol 30:422–430.

Ruby, MV; Schoof, R; Brattin, W; et al. (1999) Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessment. Environ. Sci. Technol. 33:3697-3705.

Runkel, RL; Kimball, BA; McKnight, DM; Bencala, KE (1999) Reactive solute transport in streams: A surface complexation approach for trace metal sorption. Water Resour. Res. 35(12):3829-3840.

Rusk, J.A., Hamon, R.E., Stevens, D.P., and M.J. McLaughlin. 2004. Adaptation of soil biological nitrification to heavy metals. Environ. Sci. Technol. 38:3092-97.

Ryan, P.B., K.A. Scanlon, and D.K. MacIntosh. 2001. Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. Environ. Health Perspect. 109:121-129.

Ryan, PB. (1998) Historical perspective on the role of exposure assessment in human risk assessment. In: Newman MC; Strojan, CL, eds. Risk assessment: logic and measurement. Boca Raton, FL: CRC/Lewis Press; pp. 23–43.

Sakai, T. 2000. Biomarkers of lead exposure. Ind. Health 37:127-142.

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

Salomons, W; De Rooij, NM; Kerdijk, H; et al. (1987) Sediments as sources of contaminants? Hydrobiol 149:13–30.

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

Sample, BE; Arenal, CA. (1999) Allometric models for interspecies extrapolation of wildlife toxicity data. Bulletin of Environmental Contamination & Toxicology. 62(6). 653-663.

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

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

Sample, BE; Beauchamp, JJ; Efroymson, R; Suter, GW. (1999). Literature-derived bioaccumulation models for earthworms: development and validation. Environmental Toxicology and Chemistry. 18: 2110-2120.

Sample, BE; Arenal, CA. (2001). Development of Literature-based Bioaccumulation Models for Terrestrial Arthropods. Platform presentation at 2001 SETAC Meeting in Baltimore, MD. November, 2001.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Santore, RC; Di Toro, DM; Paquin, PR. (2000) A biotic ligand model of the acute toxicity of metals: II. application to acute copper toxicity in freshwater fish and Daphnia. Environ Toxicol Chem 20(10):2397–2402

Santore, RC; Di Toro, DM; Paquin, PR; et al. (2001) Biotic ligand model of the acute toxicity of metals: 2. application to acute copper toxicity in freshwater fish and Daphnia. Environ Toxicol Chem 20:2397–2402.

Santore, RC; Mathew, R; Paquin, PR; et al. (2002) Application of the biotic ligand model to predicting zinc toxicity to rainbow trout, fathead minnow, and Daphnia magna. Comp Biochem Physiol 113C(1-2):271–286.

Santschi, PH; Nyffeler, UP; Li, Y-H. Li and P. O'Hara. (1986) Radionuclide cycling in natural waters: relevance of scavenging kinetics. In: Sediments and Water Interactions, P.G. Sly, ed., Springer Verlag, 183-191.

Santschi, PH; Amdurer, M; et al. (1987) Relative mobility of radioactive trace elements across the sediment-water interface in the MERL model ecosystems of Narragansett Bay. J Mar Res 45: 1007–1048.

Sauvé, S; Dumestre, A; McBride, M; et al. (1998) Derivation of soil quality criteria using predicted chemical speciation of Pb^{2+} and Cu^{2+}. Environ Toxicol Chem 17:1481–1489.

Saxe, JK; Impellitteri, CA; Peijnenburg, WJGM; et al. (2001) Novel model describing trace metal concentrations in the earthworm, *Eisenia andrei*. Environ Sci Technol 35:4522–4529.

Saxena, DK, R.C., Murthy, S.V. Chandra. 1989. Zinc protects testicular injury induced by concurrent exposure to cadmium and lead in rats. Res. Commun. Chem. Pathol. Pharmacol. 64:317-329.

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.

Schlekat, CE; Lee, BY; Luoma, SN. (2001) Dietary metals exposure and toxicity to aquatic organisms: implications for ecological risk assessment. In: Newman, M, ed. Coastal and estuarine risk assessment. Boca Raton, FL: CRC Press.

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

Schoof, R.A., J. Eickhoff, L.J. Yost, E.A. Crecelius, D.W. Cragin, D.M. Meacher, D.B. Menzel. 1999. Dietary exposure to inorganic arsenic. pp. 81-88. In: Proc. Third International Conference on Arsenic Exposure and Health Effects. W.R. Chappell, C.O. Abernathy, and R.L. Calderon (eds). Elsevier Science Ltd.

Schoof, R.A., L.J. Yost, J. Eickhoff, E.A. Crecelius, D.W. Cragin, D.M. Meacher, and D.B. Menzel. 1999. A market basket survey of inorganic arsenic in food. Food Chem. Toxicol. 37:839-846.

Shroeder, W.H. and Munthe, J. (1998) Atmospheric mercury - An overview. *Atmospheric Environment*, 32(5): 809-822.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Schulte, P.A. and G. Talaska. 1995. Validity criteria for the use of biological markers of exposure to chemical agents in environmental epidemiology. Toxicology 101:73-88.

Science and Research Working Group (SRWG) of the Non-Ferrous Metals Consultative Forum on Sustainable Development (RWG) (2002) Risk assesment of non-ferrous metals and sustainable development. <http://200.20.105.7/cyted-xiii/Publicaciones/Outros_Artigos/Risk Assessment_DraftReport_NFSD.doc>

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 1–6, 2002, Cardiff, Wales.

Seebaugh, D. R. and Wallace, W. G. (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 Ecology-Progress Series 272: 215-230.

Seigneur, C. and Constantinou, E.(1995). Chemical kinetic mechanism for atmospheric chromium. Environ. Sci. Technol., 29: 222-231.

Seinfeld, JH; Pandis, SN (1998) Atmospheric chemistry and physics. New York: Wiley InterScience.

Selevan, SG; Rice, DC; Hogan, KA; Euling, SY; Pfahles-Hutchens, A; Bethel, J. (2003) Blood lead concentration and delayed puberty in girls. N Engl JMed 348:(16):1527-36.

Shacklette, HT; Boerngen, JG. (1984) Element concentrations in soils and other surficial materials of the conterminous United States. Professional Paper 1270. U.S. Dept. of Interior, Geological Survey, Alexandria, VA.

Sharma, A; Srivastava, PC; Johri, BN. (1994) Contribution of VA Mycorrhiza to Zinc Uptake in Plants. IN: Manthey, J.A., D.E. Crowley, and D.G. (eds). Biochemistry of metal micronutrients in the rhizosphere Lewis Publishers, Boca Raton, FL pp. 111-124.

Sheldrake, S; Stifelman, M. (2003) A case study of lead contamination cleanup effectiveness at Bunker Hill. Sci Total Environ 303:105–23.

Siegler, R.W., D.. Nierenberg, and W.F. Hickey. 1999. Fatal poisoning from liquid dimethylmercury: A neurophathologic study. Hum. Pathol. 30 :720-3. http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=10374784.

Simkiss, K. (1983) Lipid solubility of metals in saline solutions. J Mar Biol Assoc UK 63: 1-7.

Simkiss, K. (1996) Ecotoxicants at the cell-membrane barrier. In: Newman, MC; Jagoe, CH, eds. Ecotoxicology: a hierarchical treatment. Boca Raton, FL: CRC/Lewis Publishers; pp. 59–83.

Slooff, W. (1983). Benthic macroinvertebrates and water quality assessment: some toxicological considerations. Aquat Toxicol 4:73–82.

Smit, E. (1997) Field relevance of the *Folsomia candida* soil toxicity test. Ph.D. dissertation. Vrije Universiteit, Amsterdam.

Smit, CB; Van Gestel, CM. (1998). Effects of soil type, prepercolation, and ageing on bioaccumulation and toxicity

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of zinc for the springtail *Folsomia candida*. Environmental Toxicology and Chemistry 17, No. 6, pp. 1132–1141.

Smith, CM; Wang, X; Hu, H; et al. (1995) A polymorphism in the d-aminolevulinic acid dehydratase gene can modify the pharmacodynamics and toxicity of lead. Environ Health Perspect 103:248–253.

Smolders, E., S.P. McGrath, E. Lombi., M.J. McLaughlin, M Rutgers, A. Fairbrother, L. Van der Vliet, and B. Hale. (in prep). Hazard assessment of metals and metal compounds in terrestrial systems based on persistency, bioaccumulation, and toxicity IN: Hazard Identification Approach For Metals And Inorganic Metal Substances, Adams, W.J. et al. (eds.). SETAC Press, Pensacola, FL.

Spehar, RL; Fiandt, JT. (1986) Acute and chronic effects of water quality criteria-based metal mixtures on three aquatic species. Environ Toxicol Chem 5:917–931.

Sposito, G. (1989) The chemistry of soils. New York: Oxford University Press.

Stauber, JL; Florence, TM; Gulson, BL; Dale, LS. (1994) Percutaneous absorption of inorganic lead compounds. Sci. Total Environ. 145:55-70.

Stephen, CE; Mount, DI; et al. (1985) Guidelines for deriving numerical national water quality criteria for the protection of aquatic organisms and their uses. National Technical Information Service, Springfield VA. PB 85-22-7049.

Stern, AH. (1994) Derivation of a target concentration of Pb in soil based on elevation of adult blood pressure. Risk Anal 16:201–210.

Stern, AH. (1996) Derivation of a target concentration of Pb in soil based on elevation of adult blood pressure. Risk Anal 16:201–210.

Storm, G.L., G.J. Fosmire, and E.D. Bellis. 1994. Heavy metals in the environment: Persistence of metals in soil and selected vertebrates in the vicinity of Palmerton zinc smelters J. Environ. Qual. 23:508-515.

Stumm, W. (1992) Chemistry of the solid-water interface: Processes at the mineral-water and particle-water interface. New York: Wiley InterScience.

Stumm, W; Morgan, JJ. (1996) Aquatic chemistry, 3rd ed. New York: John Wiley & Sons.

Stumm, W; Morgan, JJ (1970) Aquatic Chemistry. An Introduction Emphasizing Chemical Equilibria in Natural Waters. New York: John Wiley & Sons.

Suedel, BC; Boracxek, JA; Peddicord, RK; et al. (1994) Trophic transfer and biomagnification potential of contaminants in aquatic ecosystems. Environ Toxicol Chem 136:21–89.

Sullivan, J; Ball, J; Brick, E; et al. (1985) Report of the technical subcommittee on determination of dredge material suitability for in-water disposal. Wisconsin Department of Natural Resources, Madison, WI.

Sunderman, FW, Jr. (1978) Carcinogenic effects of metals. Fed Proc 37:40–46.

Suter, GW, II. (1993) Ecological risk assessment. Boca Raton, FL: Lewis Publishers.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Suttle, NF; Mills, CF. (1966) Studies of the toxicity of copper to pigs: 1. Effects of oral supplements zinc and iron salts on the development of copper toxicosis. Br J Nutr 20:135–149.

Swartz, RC; Dittsworth, GR; Schults, DW; et al. (1985) Sediment toxicity to a marine infaunal amphipod: cadmium and its interaction with sewage sludge. Mar Environ Res 18:133–153.

Szebedinszky, C; McGeer, JC; McDonald, DG; et al. (2001) Effects of chronic Cd exposure via the diet or water on internal organ-specific distribution and subsequent gill Cd uptake kinetics in juvenile rainbow trout (Oncorhynchus mykiss). Environ Toxicol Chem 20:597–660

Szulczewski, MD; Helmke, PA; Bleam, WF. (1997) Comparison of XANES analyses and extractions to determine chromium speciation in contaminated soils. Environ Sci Technol 31:2954–2959.

Tatara, CP; Newman, MC; Williams, P; McCloskey, JT. (1997) Predicting relative toxicity with divalent ion characteristics: *Caenorhabditis elegans*. Aquat Toxicol 39: 279-290.

Tatara, CP; Newman, MC; McCloskey, JT; Williams, PL. (1998) Use of ion characteristics to predict relative toxicity of mono-, di-, and trivalent metal ions: *Caenorhabditis elegans* LC50. Aquat Toxicol 42: 255-269.

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):1453-70.

Tessier, A. 1992. Sorption of trace elements on natural particles in oxic environments . In Environmental Particles. Edited by J. Buffle and H.P. Van Leeuwen. Lewis Publishers, Boca Raton, FL, USA. pp. 425-453.

Tessier, A; Campbell, PGC. (1987) Partitioning of trace metals in sediments: Relationships with bioavailability. Hydrobiologia 149:43–52.

Tessier, A; Campbell, PGC. (1988) Partitioning of trace metals in sediments. In: Kramer, JR; Allen, HE, eds. Metal speciation: theory, analysis and application. Chelsea, MI: Lewis Publishers; pp.183–199.

Tessier, A; Campbell, PGC; Bissom, M. (1979) Sequential extraction procedure for the speciation of particulate trace metals. Anal Chem 51:844–850.

Tessier, A; Campbell, PGC; Auclair, JC; et al. (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 41:1463–1472.

Tessier, A.; Rapin, F; Cariganan, R. (1985) Trace metals in oxic lake sediments: possible adsorption onto Iron oxyhydroxides. Geochim. Cosmochim. Ac. 49: 183-194.

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 53:1511-1522.

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. Limnology and Oceanography, 38(1):1-17.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Thawley, DG; Pratt, SE; Selby, LA. (1977) Antagonistic effect of zinc on increased urinary delta-aminolevulinic acid excretion in lead intoxicated rats. Environ Res14:463–475.

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 9:402–413.

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 & Geosciences 20:973–1023.

Tipping, E (1998) Humic ion binding model VI: An improved description of the interactions of protons and metal ions with humic substances. Aqua. Geochem. 4(1):3-48.

Tolstykh, EI; Degteva, MO; Kozheurov, VP; et al. (1998) Strontium transfer from maternal skeleton to the fetus estimated on the basis of the Techa River data. Radiat Prot Dosim 79(1–4):307–310.

Tomerlin, JR; Berry, MR; Tran, NL; et al. (1997) Development of a dietary exposure potential model for evaluating dietary exposure to chemical residues in food. J Exp Anal Environ Epidem 7:81–101.

Tsuda T., Inoue T., Kojima M. and Shigeru A. (1995) Market basket and duplicate portion estimation of dietary intakes of cadmium, mercury, arsenic, copper, manganese, and zinc by Japanese adults. Journal of AOAC International 78, 1363-1368.

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+ andZn2+ in soil pore water from the radio-labile metal fraction. Geochim. et Cosmochim. Acta 67(3):375-85.

Tyler, G; Olsson, T (2001a) Concentrations of 60 elements in the soil solution as related to the soil acidity. Eur. J. Soil Sci. 52:151-165.

Tyler, G; Olsson, T (2001b) Plant uptake of major and minor mineral elements as influenced by soil acidity and liming. Plant Soil 230:307-321.

Ullrich, S.M., Tanton, T.W., & Abdrashitova, S.A., "Mercury in the Aquatic Environment: A Review of Factors Affecting Methylation" 2001, Critical Rev. Environ. Sci. Tech. 31, 3, 241-293.

U.S. Army Center for Health Promotion and Preventative Medicine (Army). (2001). Development of Terrestrial Exposure and Bioaccumulation Information for the Army Risk Assessment Modeling System (ARAMS). Contract No. DAAD050-00-P-8365. March, 2001.

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 form the Dietary Recall (CD-ROM). Public use data file documentation number 76700. Hyattsville, MD:.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

U.S. DOE (Department of Energy). (1994) Estimating exposure of terrestrial wildlife to contaminants. ES/ER/TM-125.

U.S. FDA (U.S. Food and Drug Administration). 2001. Total diet survey. Center for Food Safety and Applied Nutrition, Office of Plant and Dairy Foods and Beverages. October. (Data summaries from 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. (2001) Distribution-based extrapolation approaches in the risk assessment of metals in the environment. Available at: http://www.icme.com/uploads/1~Fact3.pdf.

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 1:185–191.

Van Assche, F; van Tilborg, W; Waeterschoot, H. (1997) Environmental risk assessment for essential elements. Case study: Zinc. International Zinc Association, Brussels, Belgium. Available at: http://www.iza.com/zwo_org/Environment/040106.htm.

von Lindern, I; Spalinger, S; Petroysan, V; et al. (2003) Assessing remedial effectiveness through the blood lead: Soil/dust lead relationship at the Bunker Hill Superfund site in the Silver Valley of Idaho. Sci Total Environ 303:39–170.

Waalkes, M. (1995) Metal carcinogenesis. In: Goyer, RA; Klaassen, CD; eds. Metal toxicology. New York: Academic Press; pp. 47–67.

Wade, M.J., David, B.K., Carlisle, J. S. Klein, A. K. & Valoppi, L.M. “Environmental Transformations of Toxic Metals” 1993, Occup. Med. 8, 3, 575-601.

Wallace, B; Srb, A. (1961) Adaptation. Edgewood Cliffs, NJ: Prentice Hall.

Wallace, WG; Lopez, GR. (1996) Relationship between subcellular cadmium distribution in prey and cadmium trophic transfer to a predator. *Estuaries* **19**, 923-930.

Wallace, WG; Lopez, GR. (1997) Bioavailability of biologically sequestered cadmium and the implications of metal detoxification. Mar. Ecol. Prog. Ser. 147, pp. 149–157.

Wallace, WG; Lopez, GR; Levinton, JS. (1998) Cadmium resistance in an oligochaete and its effect on cadmium trophic transfer to an omnivorous shrimp. Mar. Ecol. Prog. Ser. 172:225-237.

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 Ecology-Progress Series* 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 Ecology-Progress Series* 257, 125-137.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Wang, XL. (2002) Interactions of trace metals and different marine food chains. Mar Ecol Prog Ser 243:295–309.

Wang, XL; Fisher, NS. (1999) Assimilation efficiencies of chemical contaminants in aquatic invertebrates: a synthesis. Environ Toxicol Chem 18:2034–2045.

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 515:11-28.

Washington; Washington; Wilson; eds. (2001) Physiological pharmaceutics: barriers to drug absorption, 2nd ed. New York: Taylor and Francis.

Wehrli, B; Dinkel, C; Muller, B. (1994) Measurement of benthic gradients in deep lakes with ion selective electrodes and video endoscopy. Mineral Mag 58A:961–962.

Weis, CP; LaVelle, JM. (1991) Characteristics to consider when choosing an animal model for the study of lead bioavailability. In: The proceedings of the international symposium on the bioavailability and dietary uptake of lead. Sci Technol Lett 3:113–119.

Weis, C; Hemlein, K; Drexler, J. (1992) Collection and characterization of mine waste for the purpose of determining lead bioavailability. Toxicologist 12:211.

Weis, C; Henningsen, G; Poppenga, R; et al. (1993a) Pharmacokinetics of lead in blood of immature swine following acute oral and iv exposures. Toxicologist 13:175.

Weis CP; Poppenga, R; Thacker, BJ; et al, (1993b) Systemic availability of lead (Pb^{2+}) from mineral extraction process waste to young swine: a model for human children. Abstract. Presented at Annual ASTM Meeting, Boulder, CO, Jul 26.

Welter, E; Calmano, W; Mangold, S; et al. (1999) Chemical speciation of heavy metals in soils by use of XAFS spectroscopy and electron microscopical techniques. Fr J Anal Chem 364:238–244.

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 36:264–2660.

Weltje, L. (2002) Bioavailability of Lanthanides to freshwater organisms. Speciation, accumulation and toxicity. Delft University of Technology, Delft university Press, Delft, The Netherlands.

Westall, JC, Zachary, JL; Morel, FM. (1976) A Computer Program for the Calculation of Chemical Equilibrium Composition of Aqueous Systems, Technical Note 18. Department of Civil Engineering, Massachusetts Institute of Technology, Cambridge, MA.

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. 19:1-5.

Wester RC, Hui X, Barbadillo S, Maibach HI, Lowney YW, Schoof RA, Holm SE, Ruby MV. In vivo percutaneous

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

absorption of arsenic from water and CCA-treated wood residue.Toxicol Sci. 2004 Jun;79(2):287-95.

Weston, DP; Maruya, KA. (2002) Predicting bioavailability and bioaccumulation with in vitro digestive fluid extraction. Environ Toxicol Chem 21:962–971.

White, PD; Van Leeuwen, P; Davis, BD; et al. (1998) The conceptual structure of the integrated exposure uptake biokinetic model for lead in children.Environ Health Perspect 106(Suppl. 6):1513–30.

Whitehead, D.C. 1984. The distribution and transformations of iodine in the environment. Environ. Int. 10:321-339.

WHO (World Health Organization) (1996a) Trace elements in human health and nutrition. Chapter 3: Trace element bioavailability and interactions. Geneva. pp. 23-41
.
WHO (1996b) Trace elements in human health and nutrition. Chapter 10: Manganese. Geneva. pp. 163-167.

WHO (1996c) Trace elements in human health and nutrition. Chapter 17: Arsenic. Geneva, Switzerland.

WHO/IPCS (World Health Organization/International Programme on Chemical Safety) (1981) Arsenic. Environmental Health Criteria Document No. 18. Geneva, Switzerland.

WHO/IPCS (1990a) Methylmercury. Environmental Health Criteria Document No. 101. Geneva, Switzerland.
IPCS (1990b) Beryllium. Environmental Health Criteria Document No. 106. Geneva, Switzerland.

WHO/IPCS (1991) Inorganic mercury. Environmental Health Criteria Document No. 118. Geneva, Switzerland.

WHO/IPCS (1993) Biomarkers and risk assessment: Concepts and principles. Environmental Health Criteria Document No. 155. Geneva, Switzerland.

WHO/IPCS (1995) Inorganic lead. Environmental Health Criteria Document No. 165. Geneva, Switzerland.

WHO/IPCS (1998) Copper. Environmental Health Criteria Document No. 200. Geneva, Switzerland.

WHO/IPCS (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. 183-224.

Williams, MW; Turner, JE (1981) Comments on softness parameters and metal ion toxicity. J inorg nucl Chem 43: 1689-1691.

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.

Wilson, JB. (1988) The cost of heavy-metal tolerance: an example. Evolution 42:408–413.

Winge, D; Krasno, J; Colucci, AV. (1974) Cadmium accumulation in rat liver: correlation between bound metal and pathology. In: Hoekstra, WG; Suttie, JW; Ganther, HE; et al., eds. Trace element metabolism in animals. Baltimore: University Park Press; pp. 500–502.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

Woo, ES; Monks, A; Watkins, SC; Wang, AS; Lazo, JS. (1997) Diversity of metallothionein content and subcellular localization in the National Cancer Institute tumor panel. Cancer Chemother. Pharmacol. 41:61-68.

Wu, L; Chen, J; Tanji, KK; et al. (1995). Distribution and biomagnification of selenium in a restored upland grassland contaminated by selenium from agricultural drain water. Environ Toxicol Chem 4:733–742.

Xu, GB; Yu, CP. (1986) Effects of age deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349–357.

Xu, J; Thornton, I. (1985) Arsenic in garden soils and vegetable crops in Cornwall, England: implications for human health. Environ Geochem Health 7:131–133.

Xue, H-B; Stumm, W; Sigg, L. (1988) The binding of heavy metals to algal surfaces. Water Res 22: 917-926.

Yeh, GT; Tripathi, VS (1991) A model for simulating transport of reactive multispecies components: Model development and demonstration. Water Resour. Res. 27(12):3075-3094.

Yokel, RA; McNamara, PJ. (2001) Aluminum toxicokinetics: an updated minireview. Annu Rev Pharmacol Toxicol 88:159–67.

Yokel, RA; McNamara, PJ. (2001) Aluminum toxicokinetics: an updated minireview. Annu Rev Pharmacol Toxicol 88:159–67.

Young, LB; Harvey, HH. (1991) Metal concentrations in chironomids in relation to the geochemical characteristics of surficial sediments. Arch Environ Contam Toxicol 21:202–211.

Zartarian VG, Ozkaynak H, Burke JM, Zufall MJ, Rigas ML, Furtaw EJ Jr. A modeling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and nondietary ingestion. Environ Health Perspect. 2000 Jun;108(6):505-14.

Zhang, H; Davidson, W; Miller, S; et al. (1995) In situ high resolution measurements of fluxes of Ni, Cu, Fe and Mn and concentrations of Zn and Cd in pore waters by DGT. Geochim Cosmochim Acta 59:4181–4192.

U.S. Environmental Protection Agency:

U.S. EPA. (1986a) Guidelines for the health risk assessment of chemical mixtures. Fed. Reg. 51(185):34014-14025.

U.S. EPA. (1986b) Air Quality Criteria for Lead Volumes I - IV. EPA 600/8-83-028 a-d.U.S. EPA 1992. Ground Water Issue. Behavior of Metals in Soils. EPA/540/S-92/018 October 1992

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

U.S. EPA. (1989a) Exposure factors handbook. EPA/600/8-89/043. Office of Health and Environmental Assessment.

U.S. EPA. (1989b) Risk assessment guidance for superfund (RAGS); Volume 1: human health evaluation manual (HHEM), (Part A); Interim Final. EPA 540-1-89-002, OSWER 9285.70-02B. Office of Emergency and Remedial

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Response, Washington, DC.

U.S. EPA. (1989c) Rapid bioassessment protocols for use in streams and rivers: Benthic macroinvertebrates and fish. EPA 440/4-89-001. Washington, DC.

U.S. EPA. (1989d) Sediment classification methods compendium. PB92-231679. NTIS, Springfield, VA.

U.S. EPA (1990) Methods for derivation of Inhalation Reference Concentration and Application of Inhalation Dosimetry. EPA/600/8-90/066F, Office of Research and Development, Washington D.C.

U.S. EPA (1991a) Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency. Risk Assessment Forum, Washington, DC, EPA/600/FR-91/001, 1991.

U.S. EPA (1991b) MINTEQA2, A geochemical assessment data base and test cases for environmental systems: Ver. 3.0 user's manual. EPA/600/3-91/-21. Athens, GA. Allison, JD; Brown, DS; Novo-Gradac, KJ.

U.S. EPA. (1991c) Statement of policy and guidance for petitions under Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986. Federal Register, Volume 56(100), May 23, p. 23703.

U.S. EPA. (1992a) Ground water issue: Behavior of metals in soils. EPA 540-S-92-018. October.

U.S. EPA. (1992b) Guidelines for exposure assessment. EPA/600/Z-92/001. Fed. Reg. 57(104):22888-22938.

U.S. EPA. (1992c) Dermal exposure assessment: Principles and application. EPA/600/8-91/011B.

U.S. EPA (1994a) EPA health effects notebook for hazardous air pollutants—Draft. EPA/452/D-95-003.

U.S. EPA. (1994b) Guidance Manual for the Integrated Exposure Uptake Biokinetic Model for Lead in Children. EPA/540/R-93/081, PB93-963510.

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

U.S. EPA. (1994d) Water quality standards handbook, 2nd ed. Appendix L: Interim guidance on determination and use of water effect ratios for metals. EPA-823-B-94-005a. Office of Water.

U.S. EPA. (1994b) Water quality standards handbook, 2nd ed., update #1. EPA-823-B-94-006. Office of Water.

U.S. EPA. (1995a) A guide to the biosolids risk assessments for the EPA Part 503 Rule. EPA 832-B-93-005. Office of Water, Office of Wastewater Management, Washington, DC. September.

U.S. EPA. (1995b) Final water quality guidance for the Great Lakes system; final rule. Fed. Reg. 60(56):15366-15425. March 23.

U.S. EPA. (1996a) Water quality criteria for document for the protection of aquatic life in ambient water; 1995 updates. Washington, DC, Environmental Protection Agency. EPA 820-B-96-001

U.S. EPA. (1996b) Review of the National Ambient Air Quality Standards for Particulate matter; policy assessment

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

of scientific and technical information. OAQPS Staff Paper. EPA-452/R-96-013.

U.S. EPA. (1996c) Recommendations of the technical review workgroup for lead for an approach to assessing risks associated with adult exposures to lead in soil. EPA-540-R-03-001.

U.S. EPA. (1996d) Bioavailability of arsenic and lead in environmental substrates 1. Results of an oral dosing study of immature swine. EPA 910/R-96-002 and http://www.epa.gov/r10earth/offices/oea/risk/bioavail.pdf

U.S. EPA (1997d) Progress report of the ecological committee on FIFRA risk assessment methods: VII. Terrestrial risk assessment. Available at: http:/www.epa.gov/oppefed1/ecorisk/risk.htm.

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

U.S. EPA. (1997b). Mercury study report to Congress. Office of Air and Radiation. Available at: http://www.epa.gov/oar/mercury.html.

U.S. EPA. (1997c). Air Quality Criteria for Particulate Matter. Volume I of III. EPA/600/P-95/001aF. Office of Research and Development. Washington, DC.

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

U.S. EPA. (1997e) The incidence and severity of sediment contamination in surface waters of the United States, Vol 2: Data summaries for areas of probable concern. EPA 823-R-97-007. Office of Water, Washington, DC.

U.S. EPA. (1997f) The incidence and severity of sediment contamination in surface waters of the United States, Vol 3: National sediment contaminant point source inventory. EPA 823-R-97-008. Office of Water, Washington, DC.

U.S. EPA. (1997g) Ecological risk assessment guidance for superfund: process for designing and conducting ecological risk assessments. EPA/540-R-97-006. Office of Solid Waste and Emergency Response, Washington, DC. June.

U.S. EPA. (1997h) Exposure factors handbook. EPA/600/P-95/002Fc. Office of Research and Development, U.S. EPA, Washington, DC. http://www.epa.gov/ncea/exposfac.htm

U.S. EPA. (1998a) Guidelines for ecological risk assessment. EPA 630-R-95-002F. Office of Research and Development, National Center for Environmental Assessment, Risk Assessment Forum, Washington, DC.

U.S. EPA.(1998b) Human health risk assessment protocol for hazardous waste combustion facilities. EPA 530-D-98:001.

U.S. EPA (1999a) Understanding variation in partition coefficient, Kd, values. Office of Air and Radiation. EPA 402-R-99-004A&B.

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

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

U.S. EPA. (1999c) April 6-7, 1999. *Integrated Approach to Assessing the Bioavailability and Toxicity of Metals in Surface Waters and Sediments*, a report to the EPA Science Advisory Board, Office of Water, Office of Research and Development, Washington, DC. EPA-822-E-99-001.

U.S. EPA. (1999d) IEUBK model bioavailability variable. EPA/540-F-00-006. Technical Review Workgroup for Lead, Office of Emergency and Remedial Response, Washington DC. October. http://www.epa.gov/superfund/programs/lead/products/sspbbioc.pdf

U.S. EPA. (1999e) Notice of Intent to revise aquatic life criteria for copper, silver, lead, cadmium, iron and selenium. Fed. Reg. 64(209):58409-58410. October 28.

U.S. EPA. (1999f) Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations, EPA/600/R-99/060, Office of Research and Development, Washington, DC.

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

U.S. EPA. (2000b) Supplementary guidance for conducting health risk assessment of chemical mixtures. EPA/630/R-00/002.

U.S. EPA. (2000c) Ecological soil screening level guidance; draft. Office of Emergency and Remedial Response, Washington, DC. July 10.

U.S. EPA. (2000d) Estimated Per Capita Water Ingestion in the United States. Office of Water. EPA-822-00-008. April 2000.

U.S. EPA. (2000e) "An SAB Report: Review of the Biotic Ligand Model of the Acute Toxicity of Metals," prepared by the Ecological Processes and Effects Committee of the Science Advisory Board, EPA-SAB-EPEC-00-0006.

U.S. EPA. (2001a) Description and Evaluation of Atmospheric Mercury Simulation Using the CMAQ Model; EPA/600/J-03/227.

U.S. EPA (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. OSWER 9345.0-14.

U.S. EPA. (2001c) Lead and lead compounds: Lowering of reporting thresholds; Community right-to-know toxic chemical release reporting; final rule. Fed. Reg. 66(11):4500-4547, January 17.

U.S. EPA. (2001d) User's guide for the integrated exposure uptake biokinetic model for lead in children (IEUBKwin). Office of Emergency and Remedial Response. Washington, DC.

U.S. EPA. (2001e) Integrated exposure uptake biokinetic model for lead in children (IEUBKwin v1.0). Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. (2001f) Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Interim. Office of Solid Waste and Emergency Response, Washington, D.C.. EPA/540/R-99/005. September 2001. Available at http://www.epa.gov/superfund/programs/risk/ragse/index.htm

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

U.S. EPA (2001g) Guidance for characterizing background chemicals in soil at Superfund sites; External review draft. OSWER. 9285.7-41. Office of Emergency and Remedial Response. [Replaced by Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites, EPA 540-R-01-003, September 2002.]

U.S. EPA. (2002a) Development of a framework for metals assessment and guidance for characterizing and ranking metals; draft action plan. EPA/630/P-02/003A.

U.S. EPA. (2002b) Guidance for comparing background and chemical concentrations in soil for CERCLA sites. OSWER 9285.7-41; EPA 540-R-01-003. Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. (2002c) Policy considerations for the application of background data in risk assessment and remedy selection: Role of background in the CERCLA cleanup program. OSWER 9285.6-07P. Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. (2002d) Draft action plan: Development of a framework for metals assessment and guidance for characterizing metals. EPA/630/P-02/003A. Washington, DC.

U.S. EPA. (2002e) Child-Specific Exposure Factors Handbook. Interim Final. EPA/600/P-00/002B/01

U.S. EPA. (2002f) Procedures for Deriving Equilibrium Partitioning Sediment Benchmarks (ESBs) for the Protection of Benthic Organisms: Metal Mixtures (Cadmium, Copper, Lead, Nickel, Silver, and Zinc). EPA-600-R-02-011. Office of Research and Development. Washington, DC 20460.

U.S. EPA. (2002g) Equilibrium partitioning sediment guidelines (ESGs) for the protection of benthic organisms: Metal mixtures (cadmium, copper, lead, nickel, silver and zinc). EPA-822-R-00-005.

U.S. EPA (2002h) TRIM.FaTE technical support document. Volume II: Description of chemical transport and transformation algorithms. EPA/R-02-011b. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC.

U.S. EPA (2003a) Human Health Research Strategy. Office of Research and Development, Washington, DC. September 2003. Available at: http://www.epa.gov/nheerl/humanhealth/HHRS_final_web.pdf.

U.S. EPA. (2003b) Draft final guidelines for carcinogen risk assessment. (External review draft, February 2003). EPA/630/P-03/001A, NCEA-F-0644A. Risk Assessment Forum, U.S. EPA, Washington, DC. pp. 120. Available at: http://www.epa.gov/ncea/raf/cancer2003.htm

U.S. EPA. (2003c) Guidance for the development of ecological soil screening levels. Office of Solid Waste and Emergency Response, Washington, DC. March. OSWER Directive 92857-55.

U.S. EPA. (2003d) Literature review and evaluation of the atmospheric persistence of air toxic compounds; Internal EPA Report, EPA/600/X-03/011, Research Triangle Park, NC. http://www.epa.gov/nerl/research/2003/g1-2.html.

U.S. EPA. (2003f) Reference dose for chronic oral exposure: cadmium. IRIS. Available at: http://www.epa.gov/iris/.

U.S. EPA. (2003g) Reference dose for chronic oral exposure: manganese. IRIS. Available at: http://www.epa/gov/iris/.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Note: The metals framework reference section is currently undergoing review, and revisions are anticipated.

U.S. EPA. (2003h). Estimation of Water Chemistry Parameters for Acute Copper Toxicity Tests. Office of Water, Office of Science and Technology, Health and Ecological Criteria Division, Washington, D.C.

U.S. EPA. (2003i) Saltwater Conversion Factors for Dissolved Values. Office of Water, Office of Science and Technology, Health and Ecological Criteria Division, Washington, D.C.

U.S. EPA. (2004a) Estimation of relative bioavailability of lead in soil and soil-like materials using in vivo and in vitro methods. OSWER 9285.7-77, Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA (2004b) Air Quality Criteria for Particulate Matter (External Review Draft). Office of Research and Development, National Center for Environmental Assessment. Available at: http://cfpub2.epa.gov/ncea/cfm/partmatt.cfm.

U.S. EPA (2004c) Air Toxics Risk Assessment Reference Library, Volume I. Technical Resource Manual. EPA-453-K-04-001A. OAQPS, RTP. Available at: http://www.epa.gov/ttn/fera/risk_atra_main.html.

U.S. EPA (2004d) A Discussion with the FIFRA Scientific Advisory Panel Regarding the Terrestrial and Aquatic Level II Refined Risk Assessment Models (Version 2.0). U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. March 4, 2004).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

APPENDIX

SAMPLE TABLE FOR SAB PEER REVIEW CONSIDERATION

TABLE A-1. Application of Aquatic Tools to Inorganic Metals Assessment Levels

Tools	Ranking/ Categorization	National	Site Specific
Fate and Transport	The "Unit World" model (Section 5.3.6), is being developed and should be available for use soon.	Simple models can be considered for use in screening level assessments. Sophisticated time-variable models should be used for definitive assessments. The modeling analyses should be performed by an analyst experienced in use of models and familiar with the model structure.	Simple steady-state models are appropriate for use in screening level assessments. Judicious use of conservative assumptions may provide sufficient insight to be able to decide about the need to proceed with more detailed evaluation. Complex time-variable models should be used for definitive analyses.
Trophic Transfer and Biomagnification	Because the biomagnification of inorganic metals across 3 trophic levels in aquatic systems is rare, its use in assessments is of limited value.	Because the biomagnification of inorganic metals across 3 trophic levels in aquatic systems is rare, its use in assessments is of limited value. Consideration of trophic transfer of inorganic metals is important for consumers of organisms with elevated metal burdens.	Consideration of trophic transfer of inorganic metals is important for consumers of organisms with elevated metal burdens. While it is currently difficult to include considerations of dietary toxicity of inorganic metals in aquatic assessments, it should be considered especially for detailed evaluations.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Bioaccumulation	The current state of the science does not support the use of single value BAF/BCFs as reliable indicators of acute or chronic hazard for metal substances.	Because of the complexities associated with metal bioaccumulation, it may be most appropriate to use complex models.– For example, tissue burden to exposure regression approaches, kinetic (bioenergetic based kinetic models), pharmacokinetic (multi-compartment models) and biotic ligand models. The utility and applicability of these models will vary depending on the application (e.g., screening versus definitive risk assessment) and their state of development. In addition to the above, when possible tissue burdens, critical body residues, and direct toxicity itself may be more useful in assessing bioaccumulation than modeling and other indirect approaches. In some situations/applications, it may be scientifically valid to use the BAF/BCF model or approach in metals risk assessments, for example, in site specific assessments when it is possible to account for factors outlined in bullet 2 above. In these considerations, attention should be paid to minimizing the extrapolations (e.g., across exposure concentrations, across species) and concentration dependency. Additionally, an example of how BAF/BCF data can contribute to higher level assessments in presented in Section 3.1.1. (Wildlife dietary	Because of the complexities associated with metal bioaccumulation, it may be most appropriate to use complex models.– For example, tissue burden to exposure regression approaches, kinetic (bioenergetic based kinetic models), pharmacokinetic (multi-compartment models) and biotic ligand models. The utility and applicability of these models will vary depending on the application (e.g., screening versus definitive risk assessment) and their state of development. When possible, direct measures of tissue burdens and co-located media concentraions should be used to derive site-specific bioaccumulation relationships. In some situations/applications, it may be scientifically valid to use the BAF/BCF model or approach in metals risk assessments, for example, in site specific assessments when it is possible to account for factors outlined in bullet 2 above. In these considerations, attention should be paid to minimizing the extrapolations (e.g., across exposure concentrations, across species) and concentration dependency. Additionally, an example of how BAF/BCF data can contribute to higher level assessments in presented in Section 3.1.1. (Wildlife dietary toxicity threshold).

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Ecological Effects Assessment - Water Column	Bioavailability is an essential part of all assessments. The Unit World Model (Section 5.3.6) when developed will likely be applicable to hazard-based applications	Biotic ligand modeling and FIAM type approaches may be useful to develop water quality criteria and site specific discharge and/or clean up objectives. The BLM can be used to explain variability between studies that arises because of differences in water quality. Accounting for the effect of individual water quality parameters is an approach that offers flexibility for application to specific systems or site specific locations.	FIAM and BLM approaches offer more flexibility for application to specific systems or site specific locations. Direct toxicity testing and WER approaches can be used to supplement BLM predictions in site specific assessments. The BLM is a tool for predicting acute toxicity and can be used to explain the variability between studies that arises because of differences in water quality. Accounting for the effect of individual water quality parameters is an approach that offers flexibility in terms of being adapted to specific systems or site specific locations.
Ecological Effects Assessment - Oxic Sediments	Methods not applicable to ranking.	None of the available extraction methods have been shown to be predictive of toxicity of metals in oxic sediments. Models such as EqP can be used to estimate metal concentrations in interstitial waters.	None of the available extraction methods have been shown to be predictive of toxicity of metals in oxic sediments. Site specific partition coefficients, when available, may be used to estimate metal concentrations in interstitial water. Metals may be measured directly in interstitial water and evaluated as described for anoxic sediments.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.

Ecological Effects Assessment - Anoxic Sediments	It is recommended that the use of SEM-AVS be focused on identifying sediments where direct toxicity to benthos is *not* expected (i.e., SEM-AVS < 0).	The SEM-AVS approach is the best available tool for screening analysis based solely on sediment chemistry. It is currently applicable to mixtures of copper, cadmium, zinc, lead, nickel, and silver. It is recommended that the use of SEM-AVS be focused on identifying sediments where direct toxicity to benthos is *not* expected (i.e., SEM-AVS < 0). A modification of the method is available to account for the presence of organic carbon within the sediment matrix.	The SEM-AVS approach is the best available tool for screening analysis based solely on sediment chemistry. It is currently applicable to mixtures of copper, cadmium, zinc, lead, nickel, and silver. It is recommended that the use of SEM-AVS be focused on identifying sediments where direct toxicity to benthos is *not* expected (i.e., SEM-AVS < 0). A modification of the method is available to account for the presence of organic carbon within the sediment matrix.

DISCLAIMER: This information is distributed solely for the purpose of peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA and should not be construed to represent any Agency determination or policy.