Development of a Framework for Metals Risk Assessment

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Introduction

Releases of metals and metal compounds to the environment have long been a concern for many regulatory and non-regulatory programs at the U.S. Environmental Protection Agency (USEPA) due to risks they can pose to human and ecological health. The USEPA conducts a wide range of actions to assess and manage these risks. Some of these actions include setting technology and risk-based regulatory limits on environmental releases, establishing safe levels in different environmental media, conducting screening and detailed risk assessments at site, regional, and national scales, and setting priorities for regulatory and voluntary pollution prevention actions. The challenges of assessing and managing risks associated with releases of metals and metal compounds (hereafter collectively termed "metals") are magnified by a number of attributes that are either unique or especially problematic with metals. For example, the environmental chemistry of metals is typically complex and includes the formation of different chemical species, with each metal species displaying unique chemical and physical properties. The speciation of metals in abiotic and biotic environmental media strongly influences their bioavailability, bioaccumulation and toxicity to receptor organisms. The fact that metals occur naturally in the environment raises issues regarding the treatment of natural background concentrations, acclimation and adaptation, and nutritional requirements (for essential metals) in risk assessments. In addition, the bioavailability, bioaccumulation and toxicity of metals can be strongly influenced by the presence of complexing and competing ligands, organism-specific characteristics (physiology, feeding ecology, and biology, exposure route) and other factors. In the aggregate, these and other aspects of metals behavior in the environment not only complicate assessment of their hazard and risk, but they also limit the ability to extrapolate results across metals, receptors and geographic scales.

In recognition of these and other challenges confronting the assessment and management of metals-induced risks, the Science Policy Council of the USEPA is developing a *Framework for Metals Risk Assessment* to guide future metals assessments that are conducted by the Agency. The goals of this *Framework* are: 1) to promote consistent application of scientific principles for assessing hazard and risk for metals, 2) to advance the use of state-of-the-science of methods and data, and 3) to encourage the application of a transparent process that clearly articulates the assumptions and uncertainties embedded in metals assessments. Importantly, the *Framework* recognizes and promotes the need to maintain flexibility in the analytical rigor and scope of metals assessments due to substantial differences in the statutory mandates, regulatory scope, and assessment goals among USEPA programs. In this paper, we describe the scope and process for developing the *Framework*, summarize the major scientific issues being addressed, and present the key elements of the *Framework*, which is presently under development by the USEPA.

Framework Scope

One of the first issues encountered in the process for developing the *Framework* was deciding which metals would be addressed by the *Framework* guidance. For the purpose of this paper, the term "metals" refers to elements that have been classified as metals or semi-metals (metalloids) based on their physical and chemical properties. For scientific and practical reasons, the focus of the *Framework* is on inorganic metals and metal compounds. However, the transformation processes that result in formation of organometallics will be discussed and where applicable, existing Agency guidance on the topic will be referenced. Such transformation processes are particularly important for assessments of elements such as mercury, selenium and arsenic. The *Framework* scope was also limited to non-radioactive effects of metals due to the vastly different fate, exposure, bioavailability, and toxicity processes involved in assessing risks from radioactive substances. Aside from these restrictions, the *Framework* is intended to be applicable to all other metals. However, its development and expected application are clearly focused on metals of traditional regulatory interest, some (but not all) of which include Cu, Cd, Hg, Ni, Pb, and Zn.

While the types of metals being addressed by the *Framework* have been limited to a smaller subset of metals, the breadth of regulatory assessments to which the *Framework* will apply has not been restricted. For metals, as with any other substances, Agency assessments of hazard and risk vary widely, from site-specific analyses to support decisions regarding hazardous waste site remediation to very broad national assessments that cover a large range of possible exposure situations. Within any particular type of assessment, the level of detail can vary from simplified screening analyses using default assumptions about various parameters to complex assessments relying on large amounts of data and the use of sophisticated modeling procedures. Importantly, different methods, tools, data and analytical rigor will be required depending on the type, scale and goals of the assessment. To account for such assessment-driven differences, the *Framework* is being developed in the context of three general categories of assessments, namely: 1) Site-Specific Assessments, 2) National Regulatory Assessments, and 3) National Hazard/Risk Ranking and Classification. Examples of site-specific assessments include hazardous waste site risk assessments conducted under the Superfund and Resource Conservation and Recovery Act (RCRA) programs and derivation of site-specific water quality criteria. When circumstances warrant, site-specific assessments can include application of the most detailed methods and models because data can be obtained directly from the site of interest for parameterizing and validating exposure and toxicity models.

Examples of national regulatory assessments include risk assessments and media-specific environmental criteria developed at the national level. Such assessments can either be detailed, as in the case of the USEPA's *Mercury Study Report to Congress*[1], or simplistic, as in the case of screening level assessments. In contrast with site-specific assessments, national-scale assessments often require different assumptions and methods for addressing variability in environmental and exposure conditions that occur across specific locations. One type of approach to conducting national assessments is to define one or more conservative exposure scenarios, and then conduct a detailed analysis as is done in site-specific assessments. Typically, a conservative or "high end" exposure scenario is chosen 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. Depending on the metal and degree of conservatism made in the assessment, this can be problematic for metals because the results from such scenarios can be below background levels in the environment and even nutritional requirements for essential metals. Another approach is to conduct a probabilistic analysis (such as a Monte Carlo analysis) wherein the variability of the key factors is described by parameter distributions used as inputs to the risk model. The result is an integrated distribution of potential risk levels that can account for spatial differences in metal background or species distributions. The difficulties in conducting this kind of analysis are in developing appropriate distributions for each of the parameters (particularly at a national scale), and in ensuring that adequate attention is paid to potential correlations among key parameters. The latter issue is particularly important for metals that co-occur.

Examples of national ranking and classification assessments at the USEPA include the Toxics Release Inventory (TRI) program, the Hazardous Waste Minimization program, and the New Chemicals (Premanufacture Notification program). The specific purpose of the various chemical ranking and classification procedures vary by regulatory program, but in general, they are designed to rank or classify large numbers of chemicals by selected attributes of interest (e.g., persistence, bioaccumulation, and toxicity) in order to establish priorities for future analysis, action, or information notification. In general, quantitative considerations of chemical speciation, bioavailability and exposure are difficult with national ranking and classification methods, particularly for metals, due to widely varying environmental conditions across the country, the need to be protective of many different types of organisms in different media, the lack of data, and the increased uncertainty resulting from the broad scope of these types of assessments. To be sufficiently protective, decisions about national hazard ranking and classification assessments are usually driven by available toxicity data and whether there are environmental conditions within the United States that would cause a metal to become or remain available in the environment or favor formation of bioavailable forms of the metal. While the *Framework* recognizes the Agency's regulatory needs for approaches to rank or categorize metals for various purposes, it does not develop specific guidance for how such schemes should be developed. This will be done as part of a separate effort, which is closely connected to the development of the *Framework*. Rather, the *Framework* will address the scientific principles that need to be considered when describing the attributes of metals and their subsequent aggregation into a ranking scheme.

Overview of Major Science Issues

During the process of developing the Framework for Metals Risk Assessment, the USEPA metals risk assessment workgroup identified a set of interrelated issues that will be addressed by the *Framework*. A very brief discussion of each issue is presented here. In-depth discussions of each of these topics are available in a series of five issue papers (available at: http://cfpub/epa.gov/ncea/raf/), which are described later in this manuscript.

Environmental Chemistry

As elements, metals are infinitely persistent, but can exist in different forms in the environment, transform from one form into another, or exist in different forms simultaneously. The form, or "chemical speciation" of metals varies widely depending on the environmental conditions, and is described in terms of valence (oxidation) state, chemical formulation, physical composition at various scales, and complexation with other chemicals or materials. These differences in chemical speciation affect the environmental fate, bioavailability, and environmental risk of metals[2].

Each chemical species has unique physical, chemical, and toxicological properties, which greatly complicates the assessment of environmental risk. For example, emissions of elemental mercury (Hg^0) can disperse great distances and become a part of the global atmospheric mercury pool, but oxidized mercury (e.g., mercuric chloride) dissolves in cloud water and can deposit close to an emissions source. Free Cu^{2+} ion in the water column is likely to disperse from the site of release through diffusion and through physical movement such as currents, while solid CuS is likely to settle in the sediment where it may remain for long periods of time.

For many metals, it is believed that the free ion is the dominant metal specie causing aquatic toxicity via water column exposure. Accordingly, the key parameters that affect toxicity to aquatic organisms for these metals are those that affect speciation, such as pH, redox, and binding to inorganic and organic ligands (e.g., carbonates, sulfates, dissolved organic carbon). Additionally, the toxicity of metals to aquatic organisms is also affected by other dissolved ions (e.g., Na^{1+}, Ca^{2+}) that compete with metals for binding sites on the gills or other respiratory surfaces. The combined effects of chemical speciation, competition for binding sites, and complexation with ligands have been described in a modeling framework known as the "Biotic Ligand Model" (BLM)[3,4].

In the terrestrial environment, the mobility and solubility of metals depends on numerous factors including specific physical and geochemical binding mechanisms that vary among metals and soil types[5]. Metals interact with soil through interactions with the surface of particulate material in soils (adsorption), by penetration through the particulate surfaces where the metal becomes associated with the internal material (absorption or partitioning), and through specific reactions sometimes referred to as chemisorption. Also, metals can associate with inorganic and organic ligands and precipitate. Metals can complex with inorganic soil constituents, e.g., carbonates, sulfates, hydroxides, sulfides, to form either precipitates or positively charged complexes. Both complexation and precipitation reactions are pH dependent.

Furthermore, metals can partition between soil and water media and are released into porewater[6] where they exist as charged species, as soluble complexes, or precipitate out of solution. Aging or weathering of soils can also affect the availability of many metals in soil[7]. As a result, test results obtained from freshly spiked soils may differ from those obtained from aged soils.

Bioavailability and Bioaccumulation

Bioavailability can be viewed a measure of the potential for entry of a chemical into ecological or human receptors and is specific to the receptor, the route of entry, time of exposure, and the environmental matrix containing the chemical[8]. There are many definitions of bioavailability, which are discussed in a recent National Academy of Science report[9]. Although several authors have stressed the importance of abiotic factors in aquatic and terrestrial systems on bioavailability and the influence they have on exposure[3,7,10,11], the *Framework* will also address other aspects of bioavailability, including characteristics of biota that influence uptake of metals from the environment into an organism, and distribution of metals to target tissues and cells within the organism.

Factors affecting metal bioavailability and bioaccessability include metal speciation and biotransformation, availability of complexing ligands (e.g., organic carbon, chloride, carbonate, sulfide, manganese and ferrous oxides), competition by other cations for membrane adsorption sites (e.g., calcium, magnesium), pH, redox, particle sorption, sediment and soil physicochemical properties and hydrology. Weathering or aging of metals over time also can reduce their bioavailability[6]. Risk assessments frequently are compromised by the lack of comparability in bioavailable form of the metal used for toxicity tests and those found in environmental media. Often, soluble metals salts are used in toxicity tests, which maximizes the bioavailability of the test metal, whereas environmental forms frequently are less soluble and therefore less bioavailable. Without information on the relative bioavailability of the tested material and the environmental form of the metal, accurate estimates of hazard from environmental exposures will continue to be elusive.

Additionally, many organisms undergo internal metal-protein complexation and can also form insoluble, mineralized deposits that may reach extremely high internal metal concentrations without noticeable toxic effects[12,13]. As reviewed by Wang[14], the bioavailability of these metal-enriched granules to predators of such organisms can be quite low, although indirect evidence suggests that detoxified or sequestered forms of metals may not be completely unavailable under certain circumstances.

The process of accumulating chemicals in plant or animal tissues, including metals and metal compounds, is called bioaccumulation[15,16,18]. For a given exposure condition, bioaccumulation can be viewed simply as the net result of the competing processes of chemical uptake and elimination by an organism. Although simple in concept, many factors can affect the magnitude of chemical bioaccumulation by an organism. These factors include the physicochemical properties of the chemical, the magnitude and duration of exposure, the biology, physiology and feeding ecology of the organism, and environmental factors affecting the chemical's bioavailability. With respect to metals, chemical speciation is a key determinant of bioavailability and bioaccumulation.

Biomagnification, a process whereby chemical concentrations increase in organisms of each successive trophic level, appears to be the exception rather than the rule for metals — with methylmercury (an organometallic) being one notable exception[19,20,21]. It should be noted, however, that lack of biomagnification does not imply a lack of potential to cause toxic effects. Significant risks through trophic transfer can occur in the absence of biomagnification when higher trophic level organisms are inherently more sensitive to the metal or experience greater exposure relative to lower trophic level organisms.

The growing importance of bioaccumulation in the risk assessment and regulatory process has led to considerable study over the last few decades. Unlike neutral organic chemicals where broadly applicable, mechanistically-based models for assessing bioaccumulation are available and have been applied in a regulatory capacity, analogous models for metals have yet to receive widespread regulatory application. This largely results from the highly specific nature of the bioaccumulation process with respect to different metal compounds, organisms and site conditions. As a result, there has been a reliance on empirical methods for assessing and predicting metals bioaccumulation (e.g., bioaccumulation assays, bioaccumulation factors). Some attempts have been made to generalize metals bioaccumulation across organisms, such as those quantifying the effect of body size on absorption and elimination rates for inorganic substances[22] and the use of calcium accumulation and metal-hydrogen phosphate solubility as predictors of metal bioaccumulation in freshwater mussels[23,24]. Mechanistically-based bioaccumulation models have also been developed for specific metals (e.g., Mercury Cycling Model by Hudson et al.[25], the Selenium Aquatic Toxicity Model by Bowie et al.[26], and the copper bioaccumulation in the amphipod, *Hyalella azteca* by Borgmann[27]). These models require a substantial amount of site-specific or organism-specific data to accurately predict bioaccumulation and have yet to gain widespread regulatory application.

Linking residues in tissue to adverse effects can be problematic with metals because of complications associated with their internal speciation and accumulation kinetics. In this regard, Rainbow[12] has advanced the concept that metals can exist in two separate functional "categories" (or pools) within an organism as a way of explaining observed patterns of metal bioaccumulation and toxicity in marine invertebrates. The first functional pool is considered to be 'metabolically available.' This pool is available for supporting essential functions or for exerting toxicity (when present in excess of metabolic requirements for essential metals or in excess of toxic levels for nonessential metals). The second functional pool is considered to be 'detoxified' and thus no longer available to the organism. This represents a recognized model simplification, as there is some probability that certain detoxified forms are subject to reversible processes. Nevertheless, Rainbow[12] used the model to describe various metal accumulation strategies for organisms, consisting of: 1) regulation (where metal accumulation is regulated by excretion directly from the metabolically available pool), 2) accumulation without excretion (where metal accumulation in the metabolically active pool is balanced by detoxification and storage), and 3) a combination of regulation (via excretion from the metabolically available pool or the detoxified pool) and detoxification/storage. In this model, toxicity depends on the kinetics, metabolism and distribution of the metal within an organism, rather than when a fixed body burden of total metal is reached.

The implication of these and other mechanistic aspects of metals bioaccumulation is that they can confound the interpretation and application of bioaccumulation data in metals assessments[12,13]. Specifically, regulation of essential metal residues via alteration of uptake or elimination rates, the uptake of metals through saturable processes such as binding with membrane transport proteins, the complexation and detoxification of metals by intracellular ligands, and the presence of background residues in tissues are all believed to underlie observations of a dependency of metals accumulation factors on external exposure concentration[28,29]. An accumulation factor is the ratio of a tissue concentration to the corresponding concentration in an external medium such as water or soil. As a consequence, many metals, especially essential metals, can show a decrease in their accumulation factor as the corresponding water or soil concentration increases. If the concentration dependence is strong, this will significantly limit the ability to extrapolate and apply accumulation factors across differing exposure conditions, a common need in risk assessments.

Exposure

Exposure assessment considers the route of intake of a chemical into an organism (e.g., inhalation, ingestion, dermal absorption) and the pathways that the chemical takes through the environment (e.g., via atmospheric deposition and resuspension as dust). Environmental chemistry (i.e., phase association and chemical speciation) influences both metal movement through the appropriate pathway(s), the bioavailability of the metal, and the capacity of the metal to deliver a dose to a target organ via a particular exposure route. Consequently, exposure assessment depends heavily, and builds directly on, the previous discussions of environmental chemistry and bioavailability.

For some aquatic organisms, exposure to dissolved metals and the subsequent binding of these metals to gill surfaces has been shown to be of toxicological significance. The importance of this exposure pathway has been demonstrated for several fish species and several metals, although mechanisms of toxicity differ among metals and upon exposure duration and concentration. Exposure to diet borne metals can be important relative to dissolved exposure, particularly for filter-feeding and sediment-ingesting benthic organisms; however, the toxicological significance of this exposure remains uncertain. The Biotic Ligand Model (BLM) can be used to estimate fairly accurately the amount of metal that will bind to a gill surface as a function of site-specific geochemical conditions[3]. Thus, the BLM provides a method for adjusting total water concentrations to account for site-specific environmental factors that modify bioavailablility and so provide a more realistic exposure value. Similarly, the presence and quantity of acid volatile suflides (AVS) can be used to predict the toxicological consequences of exposure to sediment-associated metals. Conceptually, when AVS exceeds the quantities of simultaneously extracted metals (SEM), metal toxicity is not expected to occur, as benthic organisms are not exposed to insoluble metal-sulfide complexes[30,31].

In terrestrial systems, the labile fraction of soil-associated metals is the fraction of toxicological significance to plants and soil invertebrates. This fraction includes metals in soil pore water and freely-exchangeable absorbed metals. An understanding of the kinetics of metal transport within the soil, adsorption to soil particles, and aging phenomena need to be better quantified to make accurate estimates of exposure. Until then, porewater concentrations are a better estimate of exposure to plants and soft-bodied soil invertebrates than are bulk soil concentrations. However, because toxicity thresholds are based on bulk soil, it will remain difficult to provide a useful, accurate figure for use in metals assessments. Wildlife and humans, on the other hand, are primarily exposed to contaminants by the oral route and dietary pathway. This necessitates understanding uptake of metals by plants and invertebrates, and the ability to transfer significant amounts into the food chain. Additionally, people are exposed through inhalation and transdermally.

Because metals do not occur singly in nature, how they interact with each other in various proportions requires a better understanding. Metal mixtures may enhance or antagonize the bioavailability of each metal, sometimes making them more available, but frequently decreasing the toxicity in face of competitive interactions for binding sites. Additionally, background concentrations of metals (either from a natural concentration or with the addition of anthropogenic diffuse sources) form a portion of the exposure of all biota. This is particularly important for essential metals, but must be considered for all metals when estimating total exposure. Because of the transient nature of some exposures (e.g., water column concentrations due to soil erosion during spring runoff), incorporation of background into regulatory practice has been difficult.

Toxicity

Toxicity, or hazard, is the *potential* for a substance to cause harm, and is the link between dose (exposure) and response (effect). Two types of health hazards exist: (1) those with a threshold for the relationship between exposure and the health effect (most target organ effects), and (2) those with non-threshold effects considered to pose some level of risk at any level of exposure (cancer and mutagenic effects). While metals primarily fall into the first group, there are a few that present cancer risks under particular exposure routes or pathways, most notably nickel (inhalation) and arsenic (drinking water)[32]. Within the USEPA, toxicity assessments and benchmark values for metals occur within the same databases as those for other compounds (e.g., the Integrated Risk Information System or "IRIS" for human health data available at http://www.epa.gov/iris and ECOTOX for aquatic and terrestrial ecological receptors available at http://www.epa.gov/ecotox).

A metal is considered essential if it is present in all healthy tissues of organisms and if its withdrawal from the body induces physiological, biochemical and structural abnormalities while its addition either reverses or prevents these abnormalities. Some elements are essential to all life (e.g., copper), and others may differ among plants and animals. The essential nature of some metals sets them apart from toxicity assessments of most xenobiotic organic chemicals, and necessitates that the reference dose or concentration (i.e., the allowable exposure to provide an adequate margin of safety below toxic effects) not be lower than the recommended daily allowance (RDA) set by the Food and Nutrition Board of the National Academy of Sciences for nutritional purposes[32]. The World Health Organization[34] also has provided guidance on methods of assessing risks from excessive exposure to nutritionally essential metals.

The metabolism and mode of toxic action of metals may be quite different from those of organic pollutants, and metals adversely impact a wider array of target tissues[35]. Often, the targets for toxicity are biochemical processes that exist at multiple sites throughout the organism and/or involve common cellular components such as membranes of cells and organelles[36]. Organs involved in the transport of metals, such as gastrointestinal tract, liver, or renal tubular cells, are particularly susceptible to toxicity owing to the higher dose received by these tissues. For some metals, toxicity results from a mechanism of action that is similar to the action of an essential element (e.g., lead activates calcium ion receptors)[37]. Moreover, metals are sometimes metabolized to less toxic forms and stored in body tissues such as bones or liver, and can be re-mobilized following pregnancy or menopause[38]. Furthermore, in addition to affecting environmental fate and exposure concentration, metal speciation can modify essentiality and toxicity. A major challenge is lack of data on specific species of metal emissions, causing assessors to compare exposure estimates with toxicity data that are not concordant for the particular metal species. A major challenge is lack of data on specific species of metal emissions, causing assessors to compare exposure estimates with toxicity data that are not concordant for the particular metal species. Such dichotomies between exposure and effects data introduce considerable uncertainty to metals risk analyses.

As commonly occurring natural elements, metals most frequently exist as mixtures. The metabolism of an essential element, such as calcium, can affect the metabolism of a non-essential toxic metal, such as lead[37]. Toxic effects of essential metals also may be a consequence of a blockage of the availability or activity of essential metals by competitive actions of toxic, non-essential metals. A competitive interaction between one or more essential metals can lead to toxic effects, such as copper toxicity being enhanced by reduced levels of molybdenum, and vice versa. Cadmium, lead and mercury in combinations or by themselves, may antagonize availability of zinc, copper and selenium when these essential elements are present in marginal amounts in the diet.

In addition to determining effects on individual organisms, ecological assessments account for changes in population growth rates, community dynamics, ecosystem functions, and biodiversity. Metal assessments are similar in most respects to those conducted for organic substances, with a few notable exceptions. Because of the natural occurrence of metals, plant and wildlife species can differ significantly in their tolerance for metals as well as in their ability to exclude or take up certain elements. Short-term acclimation also can occur. These concepts are of particular importance when designing toxicity studies, so the organisms are maintained in a soil or water environment with the appropriate background concentrations of metals prior to and during the test procedure. Differing bioavailability factors in the test medium, such as pH, organic carbon content, and cation exchange capacity, frequently confound interpretation of toxicity tests reported in the literature. As with human health studies, the metal species tested and the matrix bioavailability factors should be similar to that to which the organism is exposed. Concerns about mixtures are similar to those discussed above for human health effects.

Process for Developing the Framework

The USEPA is taking a comprehensive approach to developing the *Framework* that includes multiple opportunities for input from the general public, stakeholders, external experts, peer reviewers, and cross-agency involvement (Figure 1). The process began with the formation of a cross-Agency technical panel consisting of scientists from regulatory program and research offices within the USEPA. Key components of the *Framework* development process include producing a Metals Action Plan, a series of five issue papers on critical metals assessment topics, and draft and final versions of the *Framework for Metals Risk Assessment* (forthcoming). A brief description of each of these components follows.

Draft Metals Action Plan

In June, 2002, the USEPA Metals Assessment Workgroup published a draft Metals Action Plan (MAP)[39] that laid out the critical metals assessment issues and identified further steps in the development of the *Framework* . The draft MAP identified five general issues that are critical for metals hazard and risk assessments: chemical speciation, bioavailability, bioaccumulation, persistence, and toxicity. Within each of these issue categories, the draft MAP provided a summary of the state of the science, current Agency practice and specific issue questions that commonly are encountered in metals hazard and risk assessments (Table 1).

During the development of the draft MAP, the USEPA convened a one-day meeting to gather stakeholder input to help formulate the MAP. The meeting took place on February 20, 2002 with approximately forty stakeholders representing both industry and regulatory agencies attending. Stakeholders suggested the following organizing principles for the *Framework*. The *Framework* should:

- provide a basis for identifying and prioritizing risks to the environment that may be posed by some metals and metals species that is capable of discriminating among metals, metal alloys, and other metal compounds with respect to hazard and risk.
- be developed using sound science, and be sufficiently flexible to accommodate new methods and models as the understanding of the factors that affect the fate, transport, bioavailability, and toxicity of metal substances increases.
- allow for a tiered approach to accommodate differences in assessment purpose and availability of data.
- recognize that consideration of "inherent toxicity" alone has limited meaning with respect to metals and metal compounds, because whether an inherently toxic metal will actually induce toxicity depends on the extent of bioavailability.
- focus initially on hazard assessment as a screening mechanism while more detailed assessments for metals and metal compounds, identified in the screening process, might include life cycle and uses of metals as well as release and exposure data.

Following publication in June 2002, the draft MAP underwent review by the Agency's Science Advisory Board (SAB) in September 2002[40]. The SAB agreed that the USEPA had put forth the key scientific issues important for assessing the hazards and risks of metals and agreed that overall, metals should be assessed differently from organic pollutants in a number of contexts. The SAB provided a number of specific suggestions that are now being addressed in the *Framework*, some of which are included in Table 1.

Metals Issue Papers

Following receipt of the SAB comments, the USEPA contracted for the development of five issues papers to summarize metal-specific issues and current science related to the following topics:

- Environmental Chemistry

- Bioavailability and Bioaccumulation
- Exposure Assessment
- Human Health Effects Assessment
- Ecological Effects Assessment

Each of the issue papers is designed to capture the state-of-science for each metal-specific issue, identify what tools are available for metals assessments and which ones are under development, and provide recommendations for future research that should be taken to further reduce uncertainties. The issue paper topics, authors and affiliations are provided in Table 2. The lead authors were external experts, and USEPA and other Federal agency scientists contributed to discussions on specific topics within their individual areas of expertise or knowledge of current Agency regulatory practice. A kick-off workshop was held in December 2002 which included all the authors of the metals issue papers and other government scientists. Drafts of the metals issue papers were completed in September 2003 and are available at: http://cfpub.epa.gov/ncea/raf/. Although these papers are not official Agency documents and therefore do not necessarily reflect USEPA views of policy, the USEPA is promoting a peer review process, including a 45-day public comment period as well as an open meeting to receive verbal comments. A brief synopsis of the key elements contained in each issue paper follows.

Issue Paper on Environmental Chemistry. The draft issue paper on environmental chemistry addresses topics related to methods, models and data that are available to incorporate knowledge of environmental chemistry into metals assessments. It begins with a discussion about background levels of metals in the environment and residue-communities.the various oxidation states in which metals can be found. A discussion of the concepts of Hard Soft Acid Base (HSAB) theory provides the underpinnings for its use in other issue papers (e.g., ecological effects assessment). In brief, HSAB refers to a simple categorization scheme based on metal thermodynamics that generalizes the binding affinity of metals. Depending on a metal's HSAB qualities, it will bind to different degrees with one or more of a variety of soft to hard anions and neutral molecules. The consequence is that each metal dissolved in natural water will speciate among different forms, including the uncomplexed metal ion and various metal-ligand complexes. Effects of pH on complexing and solubility of metals is important enough to warrant its own discussion. The physicochemical factors that control adsorption and complexation of metals, as well as models that can be used to predict amounts that are complexed and/or left in solution, are presented. Methods for direct measurement of metals and metal ions in water and soil are discussed as well. The principles behind models such as the BLM and Free Ion Activity Model (FIAM)[41,42] that link metal species to toxicity in aquatic and terrestrial systems are discussed in some detail. Atmospheric chemistry of metals also is reviewed. The issue paper concludes with suggestions for how to incorporate these principles into regulatory practice; these concepts are now being incorporated into the *Framework* document.

Issue Paper on Bioavailability and Bioaccumulation. The primary goals of the issue paper on bioavailability and bioaccumulation were to summarize the state of the science supporting the assessment of metals bioavailability and bioaccumulation and to identify the relevance of this science for improving current Agency metal assessments. Five major elements of assessing metals bioavailability and bioaccumulation are described in the draft issue paper: 1) conceptual model and definitions (important for understanding the interrelationship between bioavailability and bioaccumulation processes), 2) principles common to aquatic and terrestrial systems, 3) current regulatory practices, 4) current state of the science (including human and ecological receptors), and 5) recommendations to improve future regulatory practices. The issue of concentration dependency of metals accumulation factors is discussed in depth.

Issue Paper on Exposure Assessment. The draft exposure assessment issue paper summarizes the sources, phases and exposure pathways by type of receptor (aquatic, terrestrial, human). Topics of particular focus include differences between laboratory and field exposures, methods for addressing mixtures, background concentrations, and tools for conducting exposure assessments. In addition, recommendations are provided for how to address situations where data are highly limited.

Issue Paper on Human Health Effects Assessment. The draft issue paper on human health effects discusses issues that need to be considered when conducting human health risk assessments for exposure to metals and metal compounds. The state of the science related to addressing essentiality, the role of speciation of metals and metal compounds, interactions between metals, target organ effects, and estimation of human health risks are summarized. A classification of metals based on essentiality and toxicity also is presented. This information is particularly important as risk assessors must be aware of nutritional requirements versus toxic levels.

Issue Paper on Ecological Effects Assessment. The draft ecological effects issue paper summarizes biological and ecological responses to metals and discusses the role of descriptive and predictive methods used to characterize effects of metals in risk assessment. It also examines differences in the mandates and scopes of various regulatory programs that pertain to metals in the environment. Key topics addressed include consideration of the relationship between essentiality and toxicity, physiological and toxicological responses to metals, impacts at higher levels of biological organization, use of residue-based toxicity data, and acclimation and adaptation of plants, animals, and microbial communities.

Draft and Final Framework Documents

Following the public meeting on the draft metals issue papers, the USEPA metals risk assessment workgroup will produce an interim draft of the *Framework for Metals Risk Assessment* (Figure 1). This interim draft will be the subject of a peer input workshop that will include review and comment by experts external to the USEPA. The interim draft is expected to undergo simultaneous inter-agency review under the auspices of the White House Committee on Environment and Natural Resources (CENR). Comments from both of these review activities will be addressed in second draft of the *Framework*. Concurrent with this process will be the finalization of the metals issue papers by the respective authors based on public comment. The final metals issue papers will serve as input to the second draft of the *Framework*. The second draft of the *Framework* will then be reviewed by the USEPA Science Advisory Board, the comments from which will be addressed in the final draft of the *Framework.*

Description of the Framework

The *Framework for Metals Risk Assessment* currently is under development. Its purpose is to provide a description of basic principles to be considered in assessing risks posed by metals across the Agency (e.g., site-specific and national scale assessments) and a consistent approach for use when conducting these assessments. Thus, it will lay out key scientific principles and issues, and provide tools that are currently available. Directions on strengths and shortcomings of the various tools or approaches, and descriptions of which situation(s) can benefit from particular approaches will be provided. The *Framework* will address how tools or approaches may need to be modified when conducting site-specific assessments, setting national standards or criteria, or developing ranking or classification schemes. However, the *Framework* will not be proscriptive for how any particular type of assessment should be done, as development of such detailed guidance is the purview of each USEPA program office or regulatory need.

The *Framework* will begin with a discussion of the process used to develop the information, including Science Advisory Board review and public comment and input. Metals are defined and the scope of the document will be presented. The introductory material will continue into the next section on problem formulation (i.e., characterizing the goals, scope and needs of the assessment). As with the remainder of the document, this section will point out those attributes of the assessment process that are specific to metals. The *Framework* is meant to supplement existing guidance and does not cover elements of the risk assessment process that are not unique to metals, as these are adequately addressed in other Agency guidelines[43]. A conceptual model will be presented that highlights the models and tools needed for exposure and effects analyses of metals. This section will also direct the reader through the remainder of the document (see Figure 2).

Section 3 of the *Framework* is where tools and approaches will be laid out. This will include sections on each of the topics addressed by the issue papers and summarized above. Only a brief background of why a particular issue is important for metals assessment will be provided, and the reader will be referred to the issue paper and other relevant literature for more details. The focus of this section will be primarily on the available tools and their strengths and weaknesses as applied to metals. The next section (Section 4) will put the tools into each of the three regulatory contexts (site-specific; national criteria development; ranking and categorization). Some tools can be used for all three purposes, whereas others are more directed toward particular types of assessments. Appropriate use of default values, spatial or temporal averaging, and other approaches for when data are limiting or scale precludes detailed analyses also will be discussed.

The document will conclude with a brief discussion of where current research will help reduce uncertainty in metals assessments in the near future, as well as what longer-term research could be directed. This is not intended to be an exhaustive list, but rather to provide general guidance for how to approach research planning. Again, the focus will be on metals-specific issues, not generally applicable risk assessment methods. A Literature Cited section will provide the reader with information on where to find supporting documents referenced in the *Framework*. Additional (and more comprehensive) literature reviews are available in the metals issue papers.

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Table 1. Topics and Issues Addressed in EPA's Draft Metals Action Plan

MAP Issue Category	Issue Questions	Selected SAB Comments
Chemical Speciation	• What are the most appropriate approaches for considering chemical speciation in different assessment types? • How and when should metals be appropriately grouped in hazard and risk assessments? • Should generalized exposure scenarios be adopted in metals hazard ranking and characterization protocols?	Chemical speciation should be considered broadly under the umbrella of "environmental chemistry."
Bioavailability	• How can site-specific methods be applied or adapted for addressing bioavailability to national scale assessments? • How can bioavailability differences from toxicity studies vs. environmental exposures be addressed? • How should background metals exposure be addressed in national scale assessments?	Bioavailability and bioaccumulation should be considered as an integrated concept, as bioaccumulation processes are related to bioavailability processes.
Bioaccumulation	• What methods can be used to address essentiality of metals when evaluating metals bioaccumulation data? • How should EPA interpret and apply BCF/BAF data when BCF/BAF depend on exposure concentration? • How should bioaccumulation in terrestrial organisms be quantified and expressed?	In general, bioaccumulation data are less straightforward to evaluate due to essentiality, background metals, regulation, detoxification, inverse relationship between metal exposure and accumulation, and other factors. Bioaccumulation metrics such as BCF/BAF can be problematic for generic metal hazard ranking.
Persistence	• How should environmental persistence be considered when conducting national hazard ranking and prioritization assessments? • Are there alternative methods to define persistence of metal compounds that distinguish between metals?	Stability and environmental residence time are more appropriate than the term "persistence" for characterizing temporal dynamics of metals.
Toxicity	• What methods can be used to address lack of metal compound-specific toxicity data? • Should existing risk assessment methods be modified to account for essentiality issues?	The combined effect of metals including nutritional requirements should be considered.

Table 2. Issue Papers in support of the *Framework for Metals Risk Assessment*. Found at: http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=59052.

Title	Authors	Affiliations
Environmental Chemistry of Metals	Donald Langmuir Paul Chrostowski Rufus Chaney Bernard Vigneault	Hydrochem Systems Corp./CO School of Mines CPF Associates, Inc. U.S. Department of Agriculture, CANMET Mining & Mineral Sciences Laboratories/Natural Resources Canada
Bioavailability and Bioaccumulation of Metals	John Drexler Nicholas Fisher Gerry Henningsen Roman Lanno Jim McGeer Keith Sappington	University of Colorado State University of New York H&H Scientific Services Ohio State University Natural Resources Canada NCEA, ORD, U.S. EPA
Metal Exposure Assessment	Michael C. Newman Gary L. Diamond Charles Menzie Jacqueline Moya Jerome Nriagu	College of William and Mary, VIMS Syracuse Research Corporation Menzie-Cura & Associates USEPA, ORD, NCEA University of Michigan, Ann Arbor
Human Health Effects of Metals	Robert Goyer Mari Golub	Independent Consultant, NC California EPA
Ecological Effects of Metals	Lawrence A. Kapustka William H. Clements Linda Ziccardi Paul R. Paquin Mark Sprenger Daniel Wall	**e**cological **p**lanning and **t**oxicology, inc. Colorado State University Exponent HydroQual, Inc. U.S. EPA, ERT U.S. Fish and Wildlife Service

Figure 1. Development of the *Framework for Metals Risk Assessment*

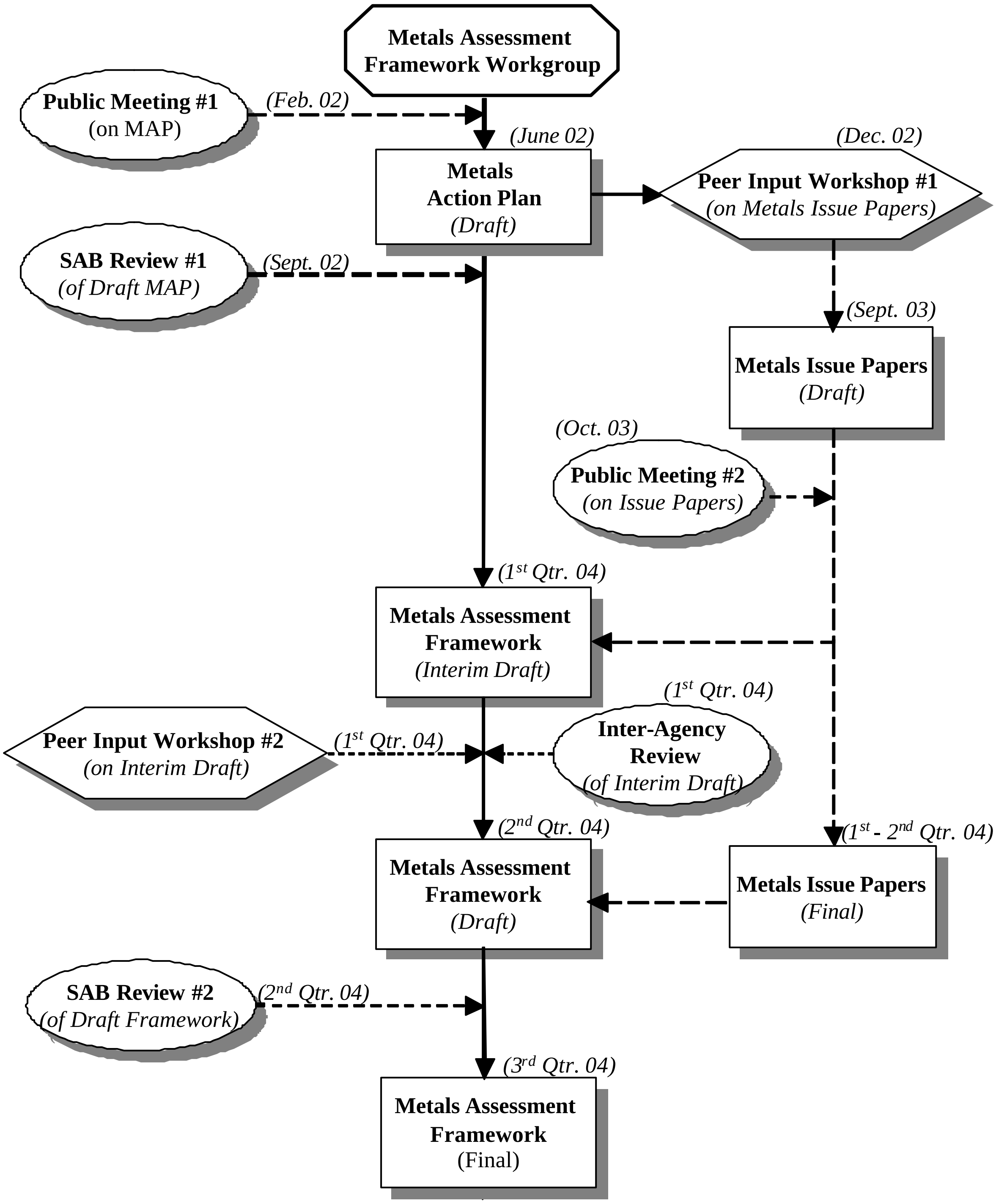

Figure 2. Outline of the *Framework for Metals Risk Assessment*

Foreward

1.0 Introduction

- 1.1 Purpose and audience
- 1.2 Scope
- 1.3 Regulatory context
  - 1.3.1 Types of Risk Analysis for Regulatory Actions
    - 1.3.1.1 National Ranking and Categorization
    - 1.3.1.2 National Regulatory Assessments
    - 1.3.1.3 Site-Specific Assessments
- 1.4 Organization

2.0 Problem Formulation

- 2.1 Conceptual Models
  - 2.1.1 Metal-specific attributes
- 2.2 Next steps

3.0 Topics of Concern

- 3.1 Environmental Chemistry
- 3.2 Exposure Pathway Analysis
- 3.3 Bioavailability
- 3.4 Characterization of Human Health Effects
- 3.5 Characterization of Ecological Effects

4.0 Regulatory Applications and Implementation of the Framework

- 4.1 Problem Formulation
- 4.2 Use of Tools for Different Types of Assessments
- 4.3 Development of the Unit World Approach
- 4.4 Risk Characterization
  - 4.4.1 Sensitive ecoystems (metalloregions)
- 4.5 Case Studies
- 4.6 General Conclusions

5.0 Research to Reduce Uncertainty

6.0 Citation