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External Review Draft

Draft Action Plan

Development of a

Framework for Metals Assessment

and

Guidance for Characterizing and Ranking Metals

Metals Action Plan Workgroup

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Executive Summary

Many EPA programs are faced with deciding whether and how to regulate toxic metals. These decisions range from setting regulatory standards for environmental releases, to establishing safe levels in different environmental media, to setting priorities for regulatory or voluntary efforts. A basic input to the decision-making process for most EPA programs is an assessment of the potential hazards and risks posed by the metal(s) to human health and the environment.

For the purpose of this document, the term "metals" refers to elements that have generally been classified as metals or semi-metals (metalloids) based on their physical and chemical properties in addition to inorganic and organic (organometallic) compounds of these elements. While in concept the range of elements and compounds encompassed by this definition is broad, in practice this action plan is focused on metals and metal compounds that are of most regulatory concern to the Agency, such as selected transition metals and semi-metals.

Assessments of potential risk incorporate different levels of detail across EPA, from site-specific analyses done to support individual permit decisions to broad national assessments which cover a large range of possible exposure situations. The level of detail can vary from simplified hazard screening analyses using default assumptions about various parameters to complex assessments relying on large amounts of data and the use of sophisticated modeling procedures.

Hazard and risk assessments of metals and metal compounds raise issues not generally encountered with organic chemicals. For example, metals are neither created nor destroyed by biological and chemical processes, rather they are transformed from one chemical species to another. Metal elements and some inorganic metal compounds are not readily soluble and as a result toxicity tests based on soluble salts may overestimate the bioavailability and the potential for toxicity for these substances. Some metals are essential elements at low levels (e.g., copper, chromium, and zinc) but toxic at higher levels; while others which are non-essential (e.g. lead, arsenic, and mercury) bioaccumulate and are toxic. Many organisms have developed mechanisms to regulate accumulation of some metals to some extent, especially for essential metals. In addition, each environmental form of the metal has its unique fate/transport, bioavailability, bioaccumulation, and toxicity characteristics. These complexities put limits on the generalizations that can be made about the hazard and risk that a metal and its compounds pose to humans and ecological systems.

In recognition of the unique assessment issues raised by metals and the complexity of addressing these issues consistently across the Agency's various programs, the Agency's Science Policy Council (SPC) tasked an Agency work group to devise an Action Plan. The goal of this Action Plan is to establish a process for developing guidance that will assure 1.) a consistent application of scientific principles for assessing hazard and risk for metals, 2.) state-of-the-science application of methods and data, 3.) A transparent process (i.e. articulating assumptions and uncertainties), and 4.) the flexibility to address program-specific issues. It includes brief descriptions of the Agency's metals assessment activities, and identifies the following critical assessment issues that need to be addressed by this cross-agency guidance:

Chemical speciation
Bioavailability
Bioaccumulation
Persistence
Toxicity

The work group recommends the development of two cross-Agency guidance documents:

A Framework for Metals Assessment

Guidance for Characterizing and Ranking Metals

The first document will be a Framework for Metals Assessment, to be completed by the end of 2003. This Framework will offer general guidance for EPA programs to use when considering the various properties of metals in assessing the hazards and risks of metals and metal compounds, such as speciation, bioavailability, bioaccumulation, persistence, and toxicity. The Framework can serve as a basis for future Agency actions.

Whereas the Framework will consider issues and principles applicable across EPA's regulatory activities, the Agency recognizes the need to take the next essential step of providing cross-Agency guidance for applying these principles. Thus, the second document will be a Guidance for Characterizing and Ranking Metals. It will provide the tools and specific guidance for characterizing and assessing the hazards and risks of metals, and it will address critical needs identified by the stakeholders. This guidance will specifically focus on delineating an assessment approach for metals and metal compounds that can differentiate when appropriate among metals and metal compounds, and can be applied in situations of priority setting, categorization, and similar activities. This document will be developed in parallel with the Framework and will follow the principles laid out in the Framework. It is anticipated that the Guidance for Characterization and Ranking of Metals will be completed within five months of completing the Framework. Together these documents should provide a reasonable, consistent, transparent, and flexible approach for assessing metals and metal compounds that can help guide Agency risk assessors and those conducting assessments for the Agency, and also provide a basis for planning future research efforts to improve the Agency's assessment methodologies for metals.

Finally, this Action Plan sets out a process that will culminate in the production of the Framework and the related Guidance for Characterization and Ranking of Metals. Public involvement and peer review are a fundamental part of this process.

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1. Background

The goal of this Action Plan is to establish a process that will assure a consistent application of scientific principles for assessing hazard and risk for metals, state-of-the-science application of methods and data, a transparent process (i.e. articulating assumptions/uncertainties), and the flexibility to address program-specific issues. For the purpose of this document, the term "metals" refers to elements that have generally been classified as metals or semi-metals (metalloids) based on their physical and chemical properties in addition to inorganic and organic (organometallic) compounds of these elements. While in concept the range of elements and compounds encompassed by this definition is broad, in practice this action plan is focused on metals and metal compounds that are of most regulatory concern to the Agency, such as selected transition metals and semi-metals.

Releases of metals and metal compounds to the environment pose concerns for many EPA programs and cause these programs to take action. These actions can range from setting regulatory standards for environmental releases, to establishing safe levels in different environmental media, to setting priorities for regulatory or voluntary efforts. A basic input to the decision-making process for most EPA programs is an assessment of the potential hazards and risks posed by the metal(s) to human health and the environment.

There has been considerable interest in the scientific assessments that the Agency conducts on metals and metal compounds as illustrated by recent events surrounding promulgation of the Toxics Release Inventory (TRI) lead rulemaking (Lead and Lead Compounds; Lowering of Reporting Thresholds; Community Right-to-Know Toxic Chemical Release Reporting; Final Rule. 66 Federal Register, 4499-4547; January 17, 2001). During the drafting of a "White Paper" by a technical panel of the Risk Assessment Forum for use in the Science Advisory Board (SAB) review of the bioaccumulation potential of lead, it became clear that the development of cross-agency guidance for assessing the hazards and risks of metal and metal compounds should be a priority for EPA. Discussions between EPA and external stakeholders as well as concerns expressed formally from the Congress, have led the Agency to develop a more comprehensive approach to metals assessments that could be the basis for future Agency actions. Therefore the Agency's Science Policy Council (SPC) has initiated a process to address the issues associated with metals that will include opportunities for external input, peer review and cross-agency involvement.

Problem Formulation - Establishing the Context for Evaluating Hazards and Risks of Metals

Assessments of hazard and risk can vary widely, from site-specific analyses to support decisions regarding hazardous waste site remediation to very broad national assessments which 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.

The first critical step for any evaluation of potential hazards and risks is Problem Formulation. For the purpose of establishing a context for this Action Plan, three different regulatory examples are presented, namely: 1) Site-Specific Assessments, 2) National Regulatory Assessments, and 3) National Hazard/Risk Ranking and Characterization. These scenarios illustrate the range of assessment scenarios which require special attention when metals are involved. We will use these examples to illustrate how technical issues may affect metal assessments. The issues summaries identify questions to address in the Framework and the Guidance for Characterization and Ranking of Metals.

Site-Specific Assessments

Site-specific assessments are typically done to inform a decision concerning a particular location. An example is an assessment to determine appropriate soil cleanup levels at a Superfund site.

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 temperature and chemistry, etc.), the existence of plants and/or animals which 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 of organisms to the metal, and the effect the metal will have on target organisms in whatever form it reaches that organism. While many of these same factors also affect the risk potential of organic chemicals, models for predicting fate, transport, and toxic properties are generally more robust for organic chemicals than for metals.

As with any type of assessment, it may be appropriate to start with a screening level analysis where variables are set to conservative default values to determine whether there is enough of a potential problem to justify proceeding with a larger data collection and analysis effort. If the screening level analysis indicates potential for unreasonable risk, a more detailed analysis might be required to support decision making.

National Regulatory Assessments

National level assessments are typically done when the Agency is setting media standards or guidelines for chemicals or other various risk-based regulations (e.g. Maximum Contaminant Levels [MCLs], National Ambient Air Quality Standards [NAAQS], Residual Risk standards for air toxics, ambient water quality criteria, Superfund soil screening levels, pesticide registrations) or when the Agency is establishing national release and/or treatment standards for industrial categories (e.g. Maximum Achievable Control Technologies [MACT] standards, effluent guidelines, hazardous waste listings). The Clean Air Act list of hazardous air pollutants includes numerous toxic metals that EPA must address through regulations and assessments. While many of these latter standards have a large technical engineering component to them, risk evaluations are sometimes conducted to ensure that the standards are appropriately protective and/or to assist in selecting cost-effective alternatives.

While differing environmental conditions among specific locations can affect the risks posed by metals or organic substances released in these locations, this variability may more significantly affect the risk estimates for metals than for organic compounds. [Note: National standards which apply at the point of exposure, such as MCLs, are less affected by these factors.] In order to do such assessments, there are several approaches the Agency commonly undertakes. One is to define one or more exposure scenarios and to conduct a relatively detailed analysis. The difficulty in this approach is in selecting the appropriate scenario; typically the Agency tries to ensure that the scenario is conservative enough to be protective of the population at highest risk (such as populations exposed above the 90th percentile) without being so conservative that the standards are protective of hypothetical individuals whose calculated risks are above the real risk distribution. In selecting the appropriate scenario, the Agency needs to consider all of the factors which may affect potential risk, including environmental factors affecting the fate, transport, exposure potential, and toxicity of the chemicals released. As has been mentioned before, these factors may have greater impacts on the estimates of risks for metals than for organic compounds.

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

National Hazard/Risk Ranking and Characterization

A third regulatory example for assessing potential hazard or risk is often used by the Agency when it is attempting to set priorities or rank chemicals for different reasons, either for regulatory activities or for other activities such as targeting voluntary pollution reduction efforts. This includes programs which look at large numbers of chemicals as well as programs that focus primarily on the inherent hazard of the chemical rather than on risk. In these cases, it is often not feasible or it is outside the scope of the program to develop quantitative risk estimates across a wide variety of potential releases as well as across the country. Therefore, the Agency may choose to identify certain attributes of chemicals which it can then use as indicators of potential risk.

Some attributes commonly used as indicators of hazard are 1) persistence, 2) bioaccumulation potential, and 3) toxicity. The reasoning behind using these indicators is that toxic chemicals that also persist and bioaccumulate are of particular concern because these properties may increase the likelihood and extent of exposure of sensitive organisms to the chemical and thus the likelihood of the chemical causing harm to the organism, or to consumers of the organism.

These indicators can be useful if they can be consistently estimated across chemicals. While the Agency recognizes that there are always exceptions, the estimation process is generally more straightforward for organics than for metals. The discussion of stakeholder comments that follows identifies several issues in applying these attributes to assessments of metals and metal compounds. Technical aspects of these and other issues are discussed in section 2.

Organic chemicals typically degrade in the environment (although the rates at which they degrade vary tremendously), so persistence is measured or estimated as the chemical’s half-life in different environmental media. When metals are viewed as elements, they are considered persistent.

These programs often consider bioaccumulation because accumulation can result in significant exposure to consumers of the organism which accumulated the chemical, or to the organism itself. While these programs use measured bioaccumulation data, they may also rely on estimation tools. Bioaccumulation potential for organic compounds in plants and animals can often be estimated using a measured or calculated octanol/water partitioning coefficient, which is an indicator of the degree to which a chemical can be absorbed by, and accumulated in, lipid tissue.

Toxicity can be based on measured values for different types of animal or plant species, or can be estimated based on structure-activity relationships. One factor that makes it comparatively straightforward to determine these properties for an organic chemical is that, if the structure of the chemical changes in the environment, then it no longer exists as that chemical and the resulting compound is evaluated as a different chemical. In fact, persistence is the indicator of the time that elapses before that process occurs.

For metals, the assignment of indicator values is more complex. A metal can exist in the environment as an element or as a compound with other inorganic or organic elements. The different metallic compounds can have significantly different properties from the element and from each other. While the element itself is infinitely persistent in the environment, its chemical form can change, and the different chemical forms can persist for different amounts of time. Different chemical forms of a metal can interchange from one form to another. This process can go on indefinitely. The specific form(s) which predominates is governed largely by prevailing environmental conditions. Also, the chemical form of a metal can affect its toxicity and its ability to bioaccumulate in the food chain. Thus, a particular chemical form that is not toxic or capable of bioaccumulating may convert to a form that can bioaccumulate or cause toxicity, and vice-versa. The ability of a metal to interconvert to different forms and the corresponding influence that the interconversion has on exposure potential and toxicity poses significant problems in ranking and characterizing metals.

Stakeholder Input

On February 20, 2002, EPA convened a one-day meeting to gather stakeholder input to help EPA formulate an Action Plan for developing the Metals Assessment Framework. Specifically, EPA solicited input on the following questions:

1. What organizing principles should the Framework follow?

2. What scientific issues should the Framework address?

3. What methods and models should be considered for inclusion in the Framework?

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

Approximately forty stakeholders representing both industry and regulatory agencies attended the meeting. With regards to Question 1 - *What organizing principles should the Framework follow?*, organizing principles for the Framework suggested by the stakeholders included the following:

- 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.

- The Framework should 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.

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

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

- The Framework should 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.

With regard to Question 2 - *What scientific issues should the Framework address?* and Question 3 - *What methods and models should be considered for inclusion in the Framework?,* the stakeholders' suggestions included the following:

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

- Valid approaches for assessing persistence should be incorporated;

- Alternative approaches for assessing bioaccumulation should be considered;

- Determine what is considered significant bioaccumulation of metals in human beings; and

- Differentiate between substances and elements.

With regard to Question 4 - *What specific steps should be taken to further involve the public and the scientific community in the development of the Framework?*, the stakeholders suggested that

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

2. Overview of Major Science Issues for the Framework

As described earlier, the assessment of metals and metal compounds presents unique challenges not generally encountered with organics in the development of an assessment framework. Based on extensive public comment during the development of the TRI Lead Rule, publications in the scientific literature, and discussions at the February 2002 stakeholder meeting, the EPA work group has identified a set of interlocking issues that will need to be addressed in developing the Framework. The following is a brief discussion of each issue. It is not the intent of this Action Plan to provide a detailed review of the science underlying each issue (that will be done in developing the Framework), rather this discussion is intended to identify the issues that must be addressed by the Framework, to frame them in the context of the scientific debate and uncertainty surrounding each issue, and to describe briefly how each issue is currently being addressed in current Agency assessments.

2.1 Chemical Speciation

As elements, metals are infinitely persistent (i.e., they are never destroyed), 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 can vary widely depending on the environmental conditions, and can be 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.

Compared to organic compounds, metals and metalloids exist in a much wider range of physical and chemical forms, and can change reversibly or irreversibly from one form to another under conditions found in the environment, or within organisms. Examples of these various forms include different valence states (e.g., Cu^0, Cu^{1+}, or Cu^{2+}), different physical states (e.g., solid $CuSO_4$ versus free Cu^{2+} in water; or gaseous elemental mercury versus oxidized mercury), in association with different ions within a physical state (e.g., solid $CuSO_4$ versus solid CuS), in different complexes (e.g., free aqueous Cu^{2+} versus Cu^{2+} complexes with dissolved or colloidal organic carbon), or even in different thermodynamic states within the same compound (e.g., amorphous FeS versus pyrite). For purposes of this discussion, this entire range of chemical forms will be referred to collectively under the term “chemical speciation.”

Each of these forms can have unique physical, chemical, and toxicological properties, which greatly complicate the assessment of environmental risk. For example, chemical form influences the fate of metals in the environment. Emissions of elemental mercury disperse great distances, becoming part of the global atmospheric 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 fall to the sediment and may remain within the sediment for long periods of time. Speciation also affects the potential for uptake by organisms; free Cu^{2+} in water binds more readily to fish gills than does CuS. Finally, speciation affects the toxicity of metals; free Cu^{2+} in water disrupts ion regulation in fish gills, while CuS does not. Also, atmospheric Cr^{6+} is a known human carcinogen, but Cr^{3+} is not. While differences in these properties are clear, it must be remembered that chemical speciation can be dynamic in the environment. For example, Cr^{6+} emissions can transform into Cr^{3+} in the atmosphere and in soils Cr^{3+} can transform to Cr^{6+}. Also, a free Cu^{2+} ion exposed to free sulfide will quickly precipitate as CuS. Alternatively, if anoxic sediment containing CuS is resuspended into the oxygenated water column, the compound may experience oxidation of the sulfide to sulfate, with concurrent release of the copper as free Cu^{2+}. Rates of such transformations vary widely as well; formation of CuS from aqueous Cu^{2+} and S^{2-} is very rapid (seconds), while oxidation/dissolution of amorphous CuS is much slower (hours to days) and even slower for mineralized CuS (covellite; years and beyond). While the above discussion focuses on copper, all metals generally show this kind of variety in chemical speciation, though the details may vary from metal to metal.

For many metals, it is believed that the free ion is the primary metal species that affects toxicity to aquatic organisms. Accordingly, the key parameters that affect toxicity to aquatic organisms for these metals are those that affect speciation, such as pH and binding to inorganic and organic ligands (e.g., dissolved organic carbon). In addition to factors that directly affect speciation, metal toxicity to aquatic organisms is also affected by other dissolved ions (e.g., Na^{1+}, Ca^{2+}) which compete with metals for binding sites on the gills or other respiratory surfaces of aquatic organisms. The combined effects of chemical speciation and competition for binding have been described in a modeling Framework known as the “Biotic Ligand Model” (BLM) as described by DiToro et al. (2001) and Santore et al. (2001).

While the water column is perhaps the most studied route of metal exposure for aquatic organisms, metals can also be taken up by aquatic organisms via the diet. While accumulation of metal by aquatic organisms via the diet is well documented, it is less clear what role dietary metals may play in actually causing toxicity. For metals such as Hg (in the methyl form) and Se, dietary exposure has critical importance in determining toxicity. For metals such as Cu, Cd, Zn, and Pb, however, the significance of dietary exposure is much less clear (e.g., compare Woodward et al., 1994 and Mount et al., 1995). Some models for the accumulation of metal by aquatic organisms have been developed (e.g., Fisher et al., 2000; Roditi et al., 2000). It does appear, however, that whole body burdens of metals may not relate directly to toxicity (e.g., Lee et al., 2000), presumably because of differences in effects occurring via dietary and waterborne exposure.

In the terrestrial environment, the mobility and solubility of contaminants depends on numerous factors including specific physical and geochemical binding mechanisms that vary among contaminants and soil types. Metals interact with soil through interactions with the surface of particulate material in soils (adsorption), by penetration through the particulate surfaces where the contaminant becomes associated with the internal material (absorption or partitioning), and through specific contaminant 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. Therefore, although these metals can form complexes with a net negative charge, under most environmentally relevant scenarios (pH = 4 to 8.5), these metals either precipitate or exist as cationic species. Contaminants can partition between soil and water media as they are released from interactions with the soil and soil constituents, thus released into the pore-water (EPA, 2000). Metals in their various forms can exist in the pore-water as charged species, as soluble complexes, or precipitate out of solution. Retention by soil is usually electrostatic with cationic species and anionic species being associated with negatively and positively charged sites on the soil, respectively. Aging or weathering of soils can also affect the availability of many contaminants in soil (Alexander, 1995; Loehr and Webster, 1996). In many instances, chemisorption and precipitation reactions during aging act to decrease the mobility and/or availability of chemicals. As a result, test results obtained from freshly spiked soils may differ from those from aged soils.

Current Agency Practice

While the risk assessment issues introduced by metal speciation are broadly recognized, the degree to which speciation is, or can be, incorporated into Agency assessments and programs varies. This is because programs vary in the degree to which fate, transport, and exposure information can be known or predicted for relevant scenarios. Examples are described below. The greatest consideration of chemical speciation generally occurs in the context of site-specific risk assessments, such as those conducted under the Superfund program.

Site-Specific Risk Assessment

Site-Specific risk assessments are conducted in support of various programs including developing cleanup alternatives on Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) sites, and similar sites administered by States, Tribes, or other programs across the country (Clay, 1991). Depending on the size and scope of the anticipated response actions, metals speciation data may be collected to provide information to refine estimates of toxicity, bioavailability, mobility, persistence, and source apportionment. If the anticipated actions are of sufficient magnitude, it may be appropriate to commit resources for more detailed investigations. Often, metals speciation data are gathered in conjunction with animal or human tests to determine bioavailability and to explore relationships between speciation and bioavailability (Casteel et al., 1997; Maddaloni et al., 1998). Concern is warranted whenever the species of the chemical of concern on the site (and the environmental and receptor characteristics) differs from the chemical used in exposure and toxicity values used to estimate risk. Many of the bioavailability/speciation studies of lead or arsenic were conducted at large mining or smelting facilities where the extensive area of contamination warranted additional studies (LaVelle et al., 1991; Davis et al., 1992, 1994; Freeman et al., 1994; Casteel et al., 1997; Maddaloni et al., 1998). Currently, estimates of bioavailability rely on empirical biological data rather than in vitro methods which are currently under development (U.S. EPA Technical Review Workgroup for Lead, 1999). Reliance on animal models limits the applicability of many bioavailability studies because of the requisite time, expertise, and expense.

National Regulatory Assessments

In other cases, the Agency conducts assessments that are intended to apply broadly, across situations where site-specific conditions may vary. Examples in this category would include national Ambient Water Quality Criteria (AWQC) intended to protect aquatic organisms from waterborne contaminants. In this case, some parameters of exposure are known (e.g., exposure is from waterborne chemical), but all site-specific factors that could affect speciation of a metal (and therefore its toxicity) are not known and/or measured.

One feature of AWQC is that they apply "instantaneously" to the chemical as it exists in the receiving water. As such, they can be based on the toxic form(s) of a metal to the extent that is known and can be measured/predicted. In this way, they do not have to directly consider changes in chemical speciation that may happen over time; they simply stipulate conditions that should not be exceeded more often than the designated exceedance frequency. While this allows AWQC to be more explicitly focused on the toxic form(s) of a metal, it does not completely sidestep the need to understand changes in chemical speciation that may occur following release of a metal. To regulate the release of metal to which the AWQC (or State standard) applies, such as in a municipal or industrial effluent, some assumptions about chemical fate must be made to relate the form and concentration of a metal in the effluent to the expected speciation in the receiving water.

Expanded consideration of chemical speciation in environmental regulation is clearly demonstrated in the evolution of AWQC for metals. When originally formulated in the early 1980's, they were applied on the basis of "total recoverable" metal in water. Although even these early criteria explicitly recognized that the toxicity of metal was affected by chemical speciation, the Agency felt at that time that these effects could not be adequately accounted for based on current science. In the early 1990's, the Agency revised this approach, based on the growing evidence that the aquatic toxicity of most metals was more directly related to the concentration of dissolved metal, rather than total recoverable. This is not to say that non-dissolved metal could not become dissolved and cause toxicity, but that the toxicity of ambient water was best assessed on the basis of dissolved metal. Today, scientific understanding of the aquatic toxicity of metals has brought the Agency to the point where AWQC for certain metals are expected to be revised and expressed on the basis of a chemical/biological model (the so-called "Biotic Ligand Model"; DiToro et al., 2001; Santore et al., 2001) that describes the expected toxicity of metal in water based on its chemical speciation, calculated from the co-occurring concentration of several organic and inorganic constituents of the water (e.g., Ca, Mg, K, Na, HCO_3^-, pH, dissolved organic carbon).

As another example, EPA also evaluates potential risks from metals in order to identify which solid wastes should be classified as hazardous under the Resource Conservation and Recovery Act (RCRA). One of the primary concerns from waste disposal is potential leaching to groundwater, so the Agency models the movement of metals leaching from a landfill environment into groundwater and then to potential drinking water wells. Since the fate and transport of metals in the subsurface environment are largely dependent on the speciation of those metals, EPA has developed models to predict changes in speciation under different subsurface conditions. For a national assessment, EPA evaluates the potential mobility of metals under a range of hydrogeological settings.

National Hazard/Risk Ranking and Characterization

One of the great challenges in national hazard and risk ranking and characterization of metals is that the context of such an assessment is generally very broad. Unlike site-specific assessments of a metal, which consider environmental conditions and speciation at a particular site, national assessments consider the many different environmental conditions that exist throughout the country, the effect these different conditions have on the fate and speciation, and the corresponding influence on the metal's availability, bioavailability and toxicity.

Some EPA programs regulate metal compounds as metal groups. One example is EPA's Toxics Release Inventory (TRI) Program, which was established under section 313 of the *Emergency Planning and Community Right-to-Know Act of 1986* (EPCRA). The TRI Program is a national, multimedia, hazard-based program, not a site-specific or media specific program. Listing of a substance onto the TRI list of toxic chemicals is generally based on the hazards of the chemical; existence of risk is generally not a pre-requisite. Under EPCRA, Congress established categories of metal compounds, such as lead compounds, copper compounds, and chromium compounds. Thus, any compound that contains lead, copper, or chromium is a listed chemical, unless it is specifically delisted or exempted as explained below. The TRI Program's policy for listing metals by category is based on the tenant that if a metal itself can cause, or reasonably can be anticipated to cause, a toxic effect, any compound that contains the metal is deemed to have satisfied the listing criteria if the EPA concludes that the metal can become available under environmental or biological conditions. The Agency has delisted specific metal compounds from EPCRA section 313 where available data show that the intact compound does not meet the toxicity criteria for listing, and that the associated metal is not available under environmental or biological (i.e., *in vivo*) conditions.

Risk assessments are also conducted for air toxics (including several metals) under the authority of Clean Air Act and related air programs. These risk assessments include residual risk assessments for specific source categories as well as various studies evaluating exposures due to multiple source types. In each case, because of data limitations, various assumptions need to be made about speciation. For example, the EPA is currently using dispersion and exposure models to estimate exposures and risks due to inhalation exposures to air toxics across the nation due to emissions from many stationary and mobile source categories. This National Scale Assessment includes several metals. Speciation is an important issue for several air toxic metals, but especially for chromium and nickel. In the initial assessment, based on limited data from a few source categories, the EPA assumed that an average of 34 percent of the chromium is in the hexavalent form. This 34% assumption was used for all sources. In the next version of the assessment, EPA plans to develop a more refined approach whereby an assumption will be made for each source category based on the limited available data for that particular source category or similar source types as well as engineering judgement. For nickel, the approach for the National Scale Assessment was based on trying to determine the fraction that is in insoluble form versus soluble form because we think the insoluble form is much more likely to be carcinogenic.

> **Issue Summary No. 2.1.1:** The environmental fate and effects of metals are heavily influenced by chemical speciation and, for that reason, explicit consideration of speciation will reduce uncertainty. At the same time, data availability will affect the degree to which Agency assessment can incorporate chemical speciation. **What approaches for considering chemical speciation are most appropriate for different assessment types (site-specific risk assessment, national assessments, ranking/prioritization)? What are the data needs for these approaches? To what degree can these approaches be extrapolated across different environmental settings, across different metals, or among different forms of the same metal?**
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> **Issue Summary No. 2.1.2:** Because metals can be converted from one chemical species to another in the environment, different compounds of the same metal are sometimes grouped for the purposes of hazard or risk assessment. For example, AWQC generally consider all forms of dissolved metal collectively. Hazard ranking schemes used by multimedia EPA programs, such as the TRI Program, consider all compounds of a particular metal collectively unless there is explicit reason not to. **Are there approaches that could be used to decide when compounds of the same metal should or should not be grouped?**
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> **Issue Summary No. 2.1.3:** In assessments such as those used for national ranking and/or prioritization, an assessment may be required to span a wide variety of potential environmental release and exposure scenarios, and consider different media, different environmental conditions, and different types of organisms, both terrestrial and aquatic. In these cases, broad generalizations about environmental fate and effects may be necessary. In some programs, the Agency addresses this challenge through the use of standardized scenarios under which potential risk is judged and/or compared. **What is the efficacy of creating generalized assessment scenarios for metals and metal compounds under other programs, such as ranking/prioritization? Under what circumstances would this be effective? What additional uncertainties would be introduced? What other approaches to evaluating chemical speciation might be applied when assessments are required for environmental situations that are highly variable or even unspecified?**

2.2 Bioavailability

Bioavailability is a measure of the potential for entry of a contaminant into ecological or human receptors and is specific to the receptor, the route of entry, time of exposure, and the environmental matrix containing the contaminant (Anderson et al., 1999). Several of the issues relating to availability of metals to aquatic organisms are discussed in the previous section on chemical speciation. To avoid duplication, this section will focus on human health and terrestrial wildlife. In this document, for human health and terrestrial wildlife, we will define bioavailability as the fraction of the oral dose that is absorbed. Thus:

$$Bioavailability \quad \frac{mass\ \ of\ \ chemical\ \ absorbed}{mass\ \ of\ \ chemical\ \ administered}$$

Concern is warranted whenever the species of a metal in a regulatory or criteria setting process (and the environmental and receptor characteristics) differs from the metal forms used in exposure and toxicity values used to estimate risk. Bioavailability is an important consideration for metals and metal compounds which are typically complexed or precipitated in the environment. The behavior and bioavailability of contaminants are greatly influenced by their interactions with environmental media, such that not all metal and metal compounds are equally available to biota. Several authors have stressed the importance of abiotic factors in aquatic and terrestrial systems on the bioavailability of contaminants and the influence they have on exposure (Linz and Nakles, 1997; Alexander, 1995; Allen et al., 1999; DiToro et al., 2001).

Relating aquatic, soil, food, and air chemistry parameters as important factors in estimating the availability of ingested metals is not a straightforward process. The percent of ingested or inhaled metal or metal compound that is absorbed is a complex issue that requires metal-specific and organism-specific data to address. Dissolution and subsequent absorption of metals in the gut or lung needs to be considered when addressing metal bioavailability. Additionally, particulate metals may be absorbed by phagocytosis. While the availability of a metal in the environment is an important factor in determining its bioavailability in aquatic species, it appears to be considerably less important in controlling its bioavailability in humans or other terrestrial species. The bioavailability of lead in humans, for example, from seemingly nonbioavailable forms is well documented. There are numerous unfortunate cases in which children have been poisoned by lead from ingestion of plaster chips that contain lead-based paint, or soils contaminated with lead from fugitive releases from nearby facilities. Lead in its neutral form is also bioavailable in humans from the inhalation route as well as the oral route of exposure. Metal compounds that have limited availability in aquatic environments may have appreciable bioavailability in humans. The main reason why the metal portions of many poorly soluble, environmentally non-dissociable metal compounds are bioavailable in humans from the oral route is due to the acidic nature of the gastrointestinal tract. Hydrochloric acid in the gastrointestinal tract of humans (and other mammals) reacts with the metal compound to form, in most cases, a metal chloride, which is usually more soluble.

From a geochemical perspective, factors affecting metal bioavailability 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. The weathering or ageing of metals over time also can reduce their bioavailability. Both adsorption and absorption partitioning processes are considered reversible, although mass transfer from the particle to the pore-water can be constrained. In the case of interactions within a particle, a contaminant can become sequestered or trapped through various physical and contaminant alterations that occur over time, such that contaminant release is completely constrained (EPA, 2000).

Menzie and Little (2000) examined the variation in the ingestion of contaminants by terrestrial wildlife. They found for some wildlife species, the accumulation of metals from food is the primary route of exposure, while for other wildlife incidental ingestion of soils is the most important exposure route for metals. In addition, the absorption of contaminants bound to incidentally ingested soil particles in the gut, is influenced by other parameters including residence time and physiology of the organism.

Another factor in evaluating the bioavailability and risk of metals to human health and wildlife is the type and availability of laboratory toxicity studies. Often, soluble metals salts are used in toxicity tests where they can maximize the bioavailability of the metal tested. There is typically little data on the relationship between the toxicity of the metal salts tested with the metals forms in environmental media or ingested by humans and wildlife. Resolution of these issues may require adjusting toxicity testing methods to address metal species, development of validated in vitro methods to estimate bioavailability, use of adjustment factors to relate toxicity data to environmental media, and the continued development of models addressing forms of metals in the environment and their toxicity.

An issue has also been raised regarding metals detoxification by certain organisms through complexation with metallothionein or formation of intra- and extracellular metal granules and the bioavailability of metals stored in these forms. Formation of these insoluble, mineralized deposits has been documented for various metals across phyla. Their formation is believed to represent a detoxification mechanism that in some cases becomes a precursor to metal excretion by the organism. Some organisms including many bivalves can store extremely high metal concentrations in the form of these intracellular metal-containing granules apparently without experiencing noticeable toxic effects. Furthermore, metals detoxification may not be an exclusive process, as some organisms apparently display a range of storage (detoxification) and regulation mechanisms (Rainbow, 1996). Thus, mechanisms for regulating or storing metals in organisms may still result in accumulation of metabolically active forms which can exert toxicity, a hypothesis advanced by (Borgmann, 1998) for explaining the lack of correlation between chronic toxicity and tissue residues of copper in the amphipod, *Hylella azteca*. While some organisms may have an ability to store metals in a form that is not toxic to the organism in which the metal is stored, it is possible that the detoxified form may be bioavailable in a consumer organism (e.g., humans) and toxic to the consumer organism.

Current Agency Practice

The Agency addresses bioavailability through the use of default values and in some cases through the development of site-specific values supported by laboratory studies. Bioavailability is not incorporated to a greater degree due to the complexity of the issues, their associated uncertainties and scientific data gaps.

Site-Specific Risk Assessments

The Office of Solid Waste and Emergency Response has published *Risk Assessment Guidance for Superfund* (RAGS), which is also applicable to site-specific risk assessments not prepared for Superfund (U.S. EPA, 1989). Other Agency publications that address site-specific risk assessments include the Residual Risk Report to Congress by the Office of Air Quality Planning and Standards. The most common treatment of bioavailability for all chemicals, including metals, is to assume that the bioavailability of the metal exposure on the site is the same as the bioavailability used to derive the toxicity value used to estimate risk. This is typically accomplished by relying on laboratory toxicity tests, which measure administered, rather than absorbed doses. Guidance for making adjustments to ensure consistent treatment of bioavailability assumptions in exposure and toxicity is included as Appendix A in RAGS. Adjustments to bioavailability may be needed to account for differences in the exposure medium, the speciation, or the route of exposure assessed at the site and the toxicity value used to predict risks.

Site-specific values may be developed if sufficient data are available (U.S. EPA, 1999). Usually, this entails conducting a well designed animal feeding study with juvenile swine identified as the preferred animal model. This has been accomplished at several sites across the country including the Murray Smelter in CO; Palmerton, PA; Jasper County, MO; Smuggler Mountain, CO; and the Kennecott site in Salt Lake City, UT.

National Regulatory Assessments

Due to the complex issues presented above and the associated uncertainties and data gaps, the application of bioavailability factors or mechanistic models in risk assessments are frequently not supported by available scientific data. While it is commonly known that bioavailability of metals in the environment may be substantially reduced due to a number of factors (e.g. complexation, precipitation, competition with environmental ligands, sorption onto soils and sediments, formation of insoluble metal compounds), screening risk assessments often assume the bioavailability of the species of metal in the assessment is the same as the bioavailability of the species of metal used to develop the toxicity value. This occurs principally because of a lack of validated data and models for assessing/predicting gut absorption of ingested metals, dissolution of ingested metals, biota specific detoxification of metals, toxicity relationship between the metal forms tested in the laboratory and the metal forms ingested, and other assessment specific factors.

Default values have been developed for some metals. For example, lead risks are typically assessed by predicting blood lead levels using the Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) developed by USEPA (U.S. EPA, 2001a). Risks protective of children are considered protective of adults, including pregnant women. The IEUBK model assigns default bioavailability factors to all lead exposure media. The default values for air, water, and soil are 32%, 50%, and 30%, respectively (U.S. EPA, 2001b).

The risk assessment to the Part 503 rule, addressing the land application of sludge, utilized almost exclusively empirical metal from soil to plant uptake data. That is, data from a variety of soils, crops, cationic exchange capacities of soils, soil pH, soil carbon, soil moisture were used. Therefore, overall bioavailability of metals from soil to crops/vegetation were automatically integrated into the exposure assessments.

National Hazard/Risk Ranking and Characterization

As was discussed in section 2.1, quantitative considerations of bioavailability are difficult due to the varying environmental conditions across the country, the need to be protective of many different types of organisms in different media, the lack of bioavailability data in organisms, and the increased uncertainty due to the broad scope of national hazard or risk characterizations. To be sufficiently protective, decisions about national hazard/risk ranking and characterization are usually driven by available toxicity data and whether there exists 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.

> **Issue Summary No. 2.2.1:** Metal bioavailability has long been recognized as being a function of environmental chemistry. Recent research has advanced the current level of understanding of metal bioavailability to aquatic life via aquatic exposures, e.g., the Biotic Ligand Model. Likewise the equilibrium partitioning approach is a way to incorporate bioavailability into the evaluation of sediment bound metals and metal compounds. To date, these approaches have been applied to site-specific assessments. **How can the Agency apply these approaches or other variants to differentiate among metals for the purposes of national regulatory standards setting or for hazard ranking and priority setting?**
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> **Issue Summary No. 2.2.2:** Although approaches to assess the bioavailability of metals in aquatic environments have been developed, the state of the science is less developed in the case of humans and wildlife. **What approaches/data should be utilized for these receptors? In particular how can bioavailability be used in hazard ranking and priority setting purposes?**

Issue Summary No. 2.2.3: Addressing bioavailability for most metals is limited principally due to lack of validated data and models for assessing/predicting gut absorption of ingested metals, dissolution of ingested metals, and biota-specific detoxification of metals. Metal and metal compound specific issues and physiological and sub-population variability of humans and terrestrial wildlife-specific issues need to be addressed. **What methods should be applied or developed to address these complex issues?**

Issue Summary No. 2.2.4: The toxicology data base utilized to assess the hazard or risk of many metals due to ingestion exposure in humans and terrestrial wildlife is largely based on test animals exposed to soluble metal salts. Relating metal speciation to toxicity in aquatic organisms is addressed in the chemical speciation section. There are typically little data on the relationship between the toxicity of the metal salts tested with the metals forms found in environmental media or ingested by humans and wildlife. Resolution of these issues may require adjusting toxicity testing methods to address metal species, use of adjustment factors to relate toxicity data to environmental media, and the continued development of models addressing forms of metals in the environment. **What methods or approaches should be applied or developed to reduce the uncertainty resulting from current methods used in mammalian toxicity tests (e.g. testing with metal forms common in the environment, development of models to relate toxicity to environmental media, or measurement of absorbed dose in toxicity tests)?**

Issue Summary No. 2.2.5: The levels of metals that commonly occur in soils are typically referred to as background. Background concentrations can vary due to soil type, depth, and region of the country. Due to this variation, background metal levels in soils are typically addressed on a site-specific basis. **When doing national level assessments, how should the Agency address background and have criteria that are conservative and protective of human health and wildlife?**

2.3 Bioaccumulation

Plants and animals accumulate many chemicals in their tissues, including metals and metal compounds, as a result of chemical exposure through external media such as water, air, food, soil, and sediment. This process is called bioaccumulation. For aquatic organisms, bioaccumulation has been defined as the net accumulation of a chemical in tissue that results from exposure to all environmental sources including water and diet (U.S. EPA, 1995; 2000a; Newman, 1998). This differs somewhat from the term bioconcentration which refers to uptake and accumulation of a chemical from water exposure only. For a given exposure condition, bioaccumulation and bioconcentration 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. Some of 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 one key determinant of bioavailability and bioaccumulation. Although the aforementioned nomenclature has been more commonly applied to aquatic organisms, the bioaccumulation process clearly applies to terrestrial organisms including humans.

Bioaccumulation itself is not a measure of an effect, adverse or otherwise. Rather, it reflects a measure of a chemical's transfer between environmental and biological compartments. For a number of chemicals and organisms, bioaccumulation is required to sustain life (e.g., for essential trace elements such as zinc and copper). In other chemical exposure situations, bioaccumulation produces residues in plants and animals that cause direct toxicity to the exposed organism and/or indirect toxicity to those organisms which consume it. Selenium is an example of an essential trace element that is both required at low concentrations but harmful to aquatic and terrestrial organisms at higher concentrations via direct and indirect (food chain) toxicity.

Some chemicals also biomagnify in aquatic food webs, a process whereby chemical concentrations increase in aquatic organisms of each successive trophic level due to increasing dietary exposures. Biomagnification appears to be restricted to certain types of organic chemicals (e.g., highly hydrophobic, poorly eliminated organic compounds) and also appears to be the exception rather than the rule for metals—with methylmercury being one notable exception (Leland and Kuwabara, 1985; Beyer, 1986; Suedel et al., 1994). In general, most inorganic forms of metals tend to biodilute in aquatic food webs, a process where tissue concentrations decrease at higher trophic levels (Suedel et al., 1994, Leland and Kuwabara, 1985). It should be noted, however, that lack of biomagnification does not automatically imply a lack of exposure from trophic transfer. Significant exposure through trophic transfer can occur in the absence of biomagnification (i.e., biomagnification factors are simply one or lower). In the case of selenium, such dietary exposures have been shown to have strong toxicological significance. A number of cationic metals can be accumulated from the dietary exposure pathway, but the toxicological significance of these exposures is still being investigated.

Bioaccumulation assessments have become integral components of many Agency chemical assessment activities. Some of these activities include risk assessments of mercury (U.S. EPA, 1997) and sewage sludge disposal practices (U.S. EPA, 1993), derivation of water quality criteria to protect human health and wildlife (U.S. EPA, 1995, 2000a), development of ecological screening criteria for soils (U.S. EPA, 2000c) and chemical hazard prioritization methodologies (U.S. EPA, 1999). Its growing importance in the risk assessment and regulatory process has also led to considerable study of bioaccumulation over the last few decades. For nonionic organic chemicals, substantial progress has been made on identifying mechanisms and factors affecting the bioaccumulation process. This research has led to the development of mechanistically-based food web models which rely on assumptions of lipid and organic carbon partitioning and measures of hydrophobicity to predict bioaccumulation across broad classes of organic compounds (Gobas, 1993; Thomann, 1989). These models have been used by EPA in the derivation of ambient water quality criteria (U.S. EPA, 1995, 2000a).

For metals and metal compounds, such broadly applicable, mechanistically-based models for assessing bioaccumulation across metal compounds have generally failed to gain widespread regulatory application. The lack of broad application of mechanistically-based models for metals largely results from the highly specific nature of the bioaccumulation process with respect to different metal compounds, organisms and site conditions. Some attempts have been made to generalize across metal compounds, such as those quantifying the effect of body size on absorption and elimination rates for inorganic substances (Hendriks and Heikens, 2001). For some specific metals, mechanistically-based bioaccumulation models have been developed (e.g., Mercury Cycling Model by Hudson et al., 1994; the Selenium Aquatic Toxicity Model by Bowie et al., 1996; copper bioaccumulation in the amphipod, *Hyalella azteca* by Borgmann, 1998; Thomann et al., 1997 for cadmium in rainbow trout). These models generally require a substantial amount of site-specific or organism-specific data to accurately predict bioaccumulation, and have yet to gain widespread regulatory application.

Current Agency Practice

The Agency currently relies on a variety of techniques to assess the bioaccumulation of metals depending on the purpose of the assessment (e.g., site-specific risk assessment, national risk assessment, national hazard/risk ranking and characterization). Common to most of these bioaccumulation assessments for metals is a strong empirical basis.

Site-Specific Risk Assessments

For site-specific assessments, methods for assessing current condition of metals bioaccumulation include direct measurement of metal residues in organisms at the study site, in addition to *in situ* and *ex situ* methods, where organisms are exposed to contaminated site media (water, sediment, soil) under field or laboratory conditions, respectively. For example, standardized tests have been developed for evaluating bioaccumulation of metals and other contaminants in sediments, including one for the oligochaete, *Lumbriculus variegatus* (ASTM, 1997). Because some species are able to regulate metals residues in their tissues and/or possess naturally high resides of certain metals, the choice of species used to monitor metal bioaccumulation is critical.

In situations where bioaccumulation must be predicted under future conditions, empirically-based accumulation factors (bioaccumulation factors, biota-sediment accumulation factors, biota-soil accumulation factors) or site-specific regression relationships (tissue residue vs. soil or sediment concentration) have been applied (e.g., Nan et al., 2002; Torres and Johnson, 2001a; Sample et al., 1999; 1998). Mechanistic approaches including bioenergetic- or physiologically-based bioaccumulation models have been used to describe and predict metals bioaccumulation, although their application to site-specific risk assessments is less common compared to empirically-based approaches. Some examples include Simas et al. (2001) for aquatic macrofauna, Saxe et al. (2001) for earthworms, Ke and Wang (2001) for oysters, and Goree et al. (1995) for cadmium bioaccumulation in terrestrial food webs.

National Regulatory Assessments

By their very nature, national regulatory assessments often lack the data necessary to incorporate all potentially important site-specific factors that can affect bioaccumulation. This aspect, combined with the lack of generalizable constructs such as those commonly used for organics (K_{ow}, lipid and organic carbon partitioning), makes national metal bioaccumulation assessments a challenging exercise. For national ambient water quality criteria designed to protect human health and wildlife, EPA typically addresses bioaccumulation of metals through the use of empirically-based bioconcentration factors (BCFs) and bioaccumulation factors (BAFs). A BCF is determined from laboratory exposures and accounts for uptake from water only. A BAF accounts for uptake from water and diet and is usually determined in the field.

Various quality guidelines have been established for evaluating BCF data, most of which are consistent with standard bioconcentration test protocols (e.g., ASTM, 1999). Because a BCF or BAF for a given chemical and organism will vary depending on the exposure duration up to the point where steady state is reached, BAF and BCF data are screened by EPA to select those values which reflect longer-term accumulation in order to approximate steady-state conditions. Since the protection goals of EPA water quality criteria are known (i.e., protection of human health or wildlife), BAFs and BCFs are selected for species and tissues that are most relevant to human and wildlife exposure. Some limited guidance is provided for evaluating BAFs and BCFs for essential metals. For example, EPA recommends that BCFs should be used only at exposure concentrations that exceed the nutritional requirements of the organism, but below levels causing adverse effects. Since bioavailability of metals (and for that matter, organic compounds) may be a concern when applying national criteria to specific sites, EPA water quality criteria encourages the development of site-specific BAFs to account for bioavailability differences between the national BAF/BCF data set and the site(s) of interest.

For establishing national ecological screening levels of metals in soil, empirically-based soil-to-biota bioaccumulation factors and regression models have been developed and applied (U.S. EPA, 2000c; Sample et al., 1999, 1998). Because variation in these factors and regression models can be substantial (spanning several orders of magnitude), conservative estimates of soil-to-biota BAFs have been used in screening applications. In general, data for developing soil-to-biota accumulation factors are far more limited compared to aquatic-based BAFs and BCFs.

National Hazard/Risk Ranking and Characterization

In the PBT frameworks used by several Agency programs, bioaccumulation is assessed primarily through the evaluation of aquatic BCF and BAF data, although chemical accumulation in humans has also been used for evaluating bioaccumulation potential. Given the broad assessment goals of the PBT frameworks (i.e., ranking chemical hazard based on all relevant exposure pathways, environmental media, and ecological and human receptors), each species for which BCF data are available is given equal weight for comparison purposes. For example, for the final lead TRI rule, lead was classified as bioaccumulative based on data from algal and bivalve species and on evidence of bioaccumulation in humans (U.S. EPA, 2001a).

Bioaccumulation Issues

This section provides a discussion of several major issues confronting the Agency with respect to interpreting and applying metals bioaccumulation data for various regulatory purposes (metals categorization/ranking, water quality criteria derivation, national and site-specific risk assessments). Several of these issues are centered on the use of BCF and BAF data for metals because of their widespread regulatory application. The major categories of metals bioaccumulation issues discussed below are:

1. Metals essentiality, regulation and interpretation of bioaccumulation data
2. Factors affecting metals bioaccumulation
3. Assessing bioaccumulation in terrestrial organisms
4. Selecting/weighting bioaccumulation data for different species
5. Interdependence of bioaccumulation and toxicity in characterizing metal hazard

Issue #1. Metals Essentiality, Regulation and Interpretation of Bioaccumulation Data

A number of metals are essential for maintaining proper biological function of terrestrial and aquatic organisms. Some metals, including sodium, potassium, calcium, magnesium, are required nutrients and serve important biological roles such as the maintenance of chemiosmotic, electrophysiological, and structural (skeletal) function. These metals tend not to be the focus of Agency regulatory and risk assessment activities. Other more toxicologically relevant metals, such as copper, chromium, nickel, and zinc, are also required micronutrients and are incorporated into various biologically important macromolecules and metalloenzymes.

As a result of their direct role in cellular function and metabolism, organisms have evolved strategies for regulating the accumulation of essential metals. One common type of accumulation strategy has been documented for certain essential metals and species. At low concentrations where organisms experience nutritional deficiency, greater uptake and retention of metals occurs in order to achieve nutritional requirements. Above their nutritional requirements, homeostasis of body burdens is maintained up to some concentration limit in the organism. Beyond this point, metal detoxification and elimination mechanisms can become saturated or disrupted thereby leading to increased accumulation and toxicity to the organism or its consumers. Importantly, this accumulation strategy is by no means universal across species (even for essential trace metals). Closely related taxa can display widely differing accumulation strategies (e.g., regulation vs. storage) as reported by Rainbow and White (1989) and Borgmann (1998).

The regulation of metals by aquatic organisms (i.e., maintenance of constant or near constant tissue concentrations over widely varying exposure concentrations) is thought to be related to the mechanism of metal uptake. For metal ions, uptake into the organism is generally thought to occur through facilitated diffusion after binding of the metal ion to membrane transport proteins or in some cases through active transport (Rainbow, 1996). Organisms display other mechanisms for altering metal accumulation, including reducing metal bioavailability via secretion of extracellular ligands, complexing metals via mucous chelation, reducing the permeability of epithelial surfaces, reducing metals transport across cell membranes, adopting behavioral modifications to avoid metal exposure and altering metal elimination rates (Mason and Jenkins, 1995).

The regulation of metals accumulation by organisms leads to difficulties when characterizing metals bioaccumulation based on simplified bioaccumulation indicators (such as the BAF or BCF commonly used for aquatic organisms) and more complex models (such as PBPK models and pharmacokinetic data commonly used for terrestrial species including humans). For example, implicit with the use of BCFs and BAFs for hazard ranking and criteria methodologies is the assumption that BCFs or BAFs are independent of external exposure concentration, at least within typical ranges encountered in the environment. This assumption essentially means that tissue residues are linearly related to exposure concentration with a zero intercept, and that the same BCF can be applied across different exposure concentrations for predicting tissue residues. For many nonionic organic chemicals where chemical uptake is believed to occur primarily via passive diffusion across biological membranes, the assumption of independence of BCF/BAF with exposure concentration has generally been accepted, although theoretical reasons exist to suggest it could be violated (e.g., when chemical metabolism is important). For metals and metal compounds, departures from the assumption of independence between the BCF (BAF) and exposure concentration have long been recognized, particularly with essential trace elements for which accumulation is regulated by many organisms (U.S. EPA, 1985; Spacie and Hamelink, 1985; Rainbow and White, 1989).

One complication associated with metals regulation is a dependency of BCFs on external exposure concentration (e.g., declining BCFs with increasing exposure concentrations). Thus, *higher BCFs* can be associated with *lower tissue residues* thereby reversing the traditional concept that higher BCFs would lead to higher exposure and risk. Observations of concentration dependency of BCFs are consistent with the notion of metal uptake via facilitated diffusion, which would be expected to result in Michaelis-Menton type saturation kinetics for metal uptake. Although BCF/concentration dependency has commonly been described for essential trace elements, it has also been documented for nonessential metals in some organisms (Brix and Deforest, 2000). This and other information suggest that the mechanisms underlying metal regulation are not necessarily specific to essential metals. Notably, concentration dependency and/or similarity of tissue residues across varying exposure concentrations does not automatically imply metal regulation. Such observations may result from artifacts of the BCF or BAF study (e.g., short-term adsorption and growth dilution).

EPA has provided limited guidance on the BCF/concentration dependency issue for deriving water quality criteria. In situations where BCFs vary with exposure concentration, early guidance recommends using the BCF from the lowest exposure concentration above the control treatment (U.S. EPA, 1985; 1995). This same guidance was adopted for hazard classification of metals, including lead under the TRI program (U.S. EPA, 2001a). EPA's updated water quality criteria guidance recommends using BCFs from concentrations that most closely align with the water quality criterion (U.S. EPA, 2000a). The basis for this recommendation involves minimizing the uncertainty when extrapolating BCFs and BAFs across different exposure concentrations between the BCF study and its application for deriving a particular criterion. In theory, such an approach might use an allowable dietary intake concentration (determined from the toxicity and exposure data) and the concentration-tissue residue relationship derived from the BCF test to identify the ambient concentration that is most suitable for estimating the BCF. However, this guidance has not yet been applied for deriving criteria.

The existence of inverse relationships between BCF (BAF) and exposure concentrations for certain metal/species combinations has led to recommendations by some to abandon the current use of BCFs and BAFs for classifying metal hazards (Adams, 2000; Brix and Deforest, 2000). The OECD has recently published guidance for classifying metals that are hazardous to aquatic environments (OECD, 2001). The hazard classification schemes presented in the guidance incorporate, among other parameters, evidence of bioaccumulation as a basis for hazard ranking. The guidance advises, however, that in situations in which there is an inverse relationship between BCF and external water concentration the bioconcentration data should be used with care.

> **Issue Summary No. 2.3.1:** Essentiality and subsequent regulation of metal accumulation by organisms complicate the interpretation and application of metals bioaccumulation data for aquatic and terrestrial organisms. **What approaches for considering essentiality of metals are appropriate for evaluating metals bioaccumulation data for aquatic and terrestrial species? When BAF/BCF values depend on exposure concentration, can such data be reliably interpreted and applied in different regulatory scenarios (metal characterization/ranking, criteria derivation, site-specific & national assessments)? If so, what approaches are best for interpreting and applying these data?**

Issue #2. Factors Affecting Bioaccumulation

Besides the magnitude and duration of exposure, the bioaccumulation of a particular metal by an aquatic or terrestrial organism can be affected by many factors. Most of these factors relate to the biogeochemistry of the metal in the environment and the biological, physiological or ecological characteristics of the organism of concern. From a geochemical perspective, factors affecting metal bioaccumulation 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. From an organism perspective, some important factors include its age or size, life stage, feeding ecology, health or physiological condition, availability and/or induction of detoxification mechanisms, exposure route and reproductive status.

Among these various factors affecting metals bioaccumulation, metal speciation is particularly important because it defines the reactivity of chemical compound(s) involved in the assessment. Because speciation and bioavailability can differ widely from the laboratory to the field, concerns have been raised as to the applicability of laboratory-based BCFs to field conditions. For example, laboratory studies of bioconcentration typically use soluble metal salts in relatively clean water. In the field, metals may transform into less soluble species or may be complexed with ligands thereby reducing their bioaccumulation relative to laboratory tests. In the case of mercury, bioaccumulation can be enhanced in the field relative to the laboratory due to the biotransformation of inorganic mercury into methylmercury, which has significantly higher bioavailability. Even with field-based BAFs, extrapolation of results from one site to another involves uncertainty because of differences in bioavailability across sites and ecosystems.

While much is known about various factors which can affect metals bioaccumulation, the current ability to incorporate such factors into estimates or predictions of metal bioaccumulation is limited, particularly in national or regional applications where site-specific data are typically sparse. In site-specific applications, factors affecting bioaccumulation can be incorporated directly through empirical approaches (i.e., site-specific BAFs) or in some cases, through the calibration and application of mechanistically-based models given sufficient resources. For national or regional assessments, progress has been made in addressing bioavailability of metals for predicting acute toxicity to aquatic organisms (e.g., development of the SEM/AVS and Biotic Ligand Model (BLM) methodologies, U.S. EPA, 2000d, Di Toro et al., 2001). Although these models do not explicitly predict bioaccumulation, they do represent critical advancements in addressing metal bioavailability and toxicity, which are likely to be applicable to bioaccumulation assessments.

> **Issue Summary No. 2.3.2:** Numerous factors can affect the bioaccumulation of metals by aquatic organisms. Unlike nonionic organic chemicals where certain physicochemical parameters have been successfully applied for improving predictions of chemical bioaccumulation (e.g., K_{ow}, lipid content, organic carbon fraction), analogous procedures for improving estimates of metals bioaccumulation typically have not been developed or widely applied in most EPA regulatory activities. In some cases, this limitation has led to substantial uncertainty in the extrapolation of BAFs and BCFs across locations and species, as illustrated by EPA's evaluation of BAFs for methylmercury (U.S. EPA, 2001b). **Given the present state of the science with respect to metals bioaccumulation, to what extent can the Agency use current or emerging approaches to incorporate factors affecting bioaccumulation by aquatic organisms for improving the estimation and prediction of metals bioaccumulation? This issue is particularly important in the context of regional or national-level assessments where broad scale generalizations are necessary.**

Issue #3. Assessing Hazard from Bioaccumulation in Terrestrial Organisms

The U.S. EPA's PBT framework used by the TRI program currently relies on aquatic bioaccumulation data (e.g., BCFs, BAFs) and human bioaccumulation data for classifying chemicals according to their bioaccumulative properties (64 FR pages 58666-58753; October 29, 1999 and 66 FR pages 4500-4547, January 17, 2001). Bioaccumulation metrics analogous to the BCF or BAF are not available for mammals and humans, nor might they be appropriate. The advantage of expressing bioaccumulation in terms of BAF or BCF is that these terms serve as a simple and practical way of representing the complex phenomena of bioaccumulation, just as octanol/water partition coefficient (log K_{ow}) is a practical and simple way of expressing a substance's lipophilicity. The reliance on aquatic bioaccumulation data is due in part to the widespread use and availability of BCFs and BAFs for toxic chemicals, including metals. The BCF and BAF descriptors enable one to delineate or express more precisely the degree to which a chemical bioaccumulates in an organism, and facilitates distinctions in ranking: e.g., "bioaccumulative versus highly bioaccumulative." Such delineations and distinctions cannot be made as effectively by mental intuition or qualitative analysis of data.

Despite a strong focus on aquatic-based bioaccumulation data for hazard classification purposes, the Agency clearly recognizes the importance of bioaccumulation in terrestrial organisms, including humans. For some chemicals, bioaccumulation and subsequent exposure of human and ecological receptors via the terrestrial food web may be of equal or greater concern compared to the aquatic pathway. For example, human exposure via dietary sources associated with the terrestrial food web is considered important for dioxin and dioxin-like compounds (U.S. EPA, 2000b).

Various types of data and approaches have been used to characterize bioaccumulation by terrestrial organisms. Some of these data include soil-to-biota concentration factors and associated regression models for earthworms, plants, and small mammals. Recently, the Agency has compiled such terrestrial bioaccumulation data for use in estimating ecologically-based soil screening levels for organic and metal compounds (U.S. EPA, 2000c). Mechanistically-based models have also been developed and evaluated for predicting bioaccumulation by terrestrial organisms (e.g., Saxe et al., 2001 for earthworms; Torres and Johnson, 2001b for small mammals). The earthworm bioaccumulation model developed by Saxe et al (2001) appears promising, although independent validation of the model was not possible due to lack of appropriate data. As discussed by Torres and Johnson (2001b), many of the bioaccumulation models developed for small mammals have achieved mixed success in terms of predictability.

Besides bioaccumulation data collected under natural exposures in the field, a large pharmacokinetic data base exists for many specific types of mammals exposed under laboratory conditions. Pertinent data are also available for humans from occupational or clinical exposures. These data consist chiefly of organ or tissue concentrations of chemicals that result from exposures of different routes, durations, sources and pathways. Unlike bioaccumulation data measured in aquatic species, laboratory-based mammalian bioaccumulation data are not expressed in terms of BCF or BAF because these terms are derived from exposure conditions that are generally not consistent with those used to expose mammals (e.g., dietary, dermal, intravenous, inhalation, drinking water exposures). While much data pertaining to the bioaccumulation of substances, including metals, in humans and other mammals are available, there currently are no universally accepted indices of these data. Interpretation and utilization of mammalian bioaccumulation data during hazard assessments of substances are usually made qualitatively. This makes the characterization of the bioaccumulative properties of a substance in mammals more subjective, and ranking more difficult.

The lack of indices or a more descriptive approach for expressing bioaccumulation of chemicals in mammals notwithstanding, mammals (including humans) can and do bioaccumulate chemicals and EPA programs need to consider this when making decisions regarding the bioaccumulative properties of a chemical. For example, in selecting toxic endpoints for human health risk assessments of pesticides, EPA's Office of Pesticide Programs (OPP) evaluates toxicity data measured in rodents and other animals. As part of these hazard evaluations of pesticides, OPP toxicologists look for evidence of bioaccumulation from pharmacokinetic studies, such as animal metabolism studies. Evidence of bioaccumulation would include elevated tissue concentrations of pesticide residues in tissues of test animals following exposure. Pesticide substances that have, or appear to have bioaccumulative properties of concern may be assigned more protective endpoints. The assessment of bioaccumulative properties of pesticides in animals is done qualitatively, but a more descriptive method for assessing pharmacokinetic data to draw conclusions regarding bioaccumulative properties of pesticides would be preferable. For the TRI Lead Rule (U.S. EPA, 2001a), bioaccumulation of lead in humans was considered in the evaluation of lead as a PBT.

> **Issue Summary No. 2.3.3:** EPA's current hazard evaluation methodologies currently rely heavily on aquatic bioaccumulation data (e.g., BCFs, BAFs) to classify chemicals according to their bioaccumulative properties. Bioaccumulation of metals is also relevant to terrestrial organisms. **Given the importance of metal bioaccumulation in the terrestrial ecosystems, how can the Agency apply existing and emerging tools used to quantify bioaccumulation in terrestrial organisms for estimating and ranking bioaccumulation hazard potential of metals? Specifically, how can the Agency better use and interpret mammalian pharmacokinetic data, including human data, to characterize bioaccumulation for hazard ranking purposes? Are there reliable ways in which mammalian pharmacokinetic data can be represented in the form of indices that are analogous to BCF and BAF for aquatic species?**

Issue #4. Selecting/Weighting Bioaccumulation Data for Different Species

Bioaccumulation of chemicals (including metals and metal compounds) is of concern because it provides a mechanism to amplify the exposure of humans and other organisms to chemicals released to the environment. Many bioaccumulation studies are conducted with fish and shellfish species, presumably because these organisms have clear connectivity to consumption by humans, as well as aquatic and terrestrial-based predators. For some chemicals, bioaccumulation data are available for other organisms, such as algae, or benthic macroinvertebrates other than shellfish, which must be factored into a decision regarding the bioaccumulative potential of a chemical. Some chemicals show a propensity to accumulate in certain groups to a greater degree than in others.

When conducting a risk assessment and deriving chemical criteria, knowledge of the receptor organism(s) and its prey base greatly informs the choice of species from which to evaluate and assess bioaccumulation. For human health criteria derivations, choice of species and tissues from which bioaccumulation is assessed includes consideration of their representativeness of organisms consumed by humans. Similarly considerations are made in the derivation of wildlife criteria, where whole-body residues are preferred over other tissue types such as fillets. The scope of typical risk assessments and criteria derivations also provides the opportunity to link bioaccumulation data with the most appropriate metrics of exposure (e.g., consumption patterns and rates) and toxicity (e.g., ingestion-based toxicity values).

In the case of hazard assessment (e.g., EPA's PBT Framework), the broad assessment goals (e.g., ranking hazard relative to all ecological and human receptors) render the choice of species from which to evaluate bioaccumulation ambiguous. When few bioaccumulation data are available, it would seem prudent to consider any high BCF as evidence for bioaccumulation concern regardless of the organism, since in this case there are no data for most organisms and the existence of bioaccumulation in one organism is reason to presume its existence in others.

For chemicals having substantial bioaccumulation data, patterns in the bioaccumulation data may be evident. For lead, bioaccumulation occurs to some degree in a variety of aquatic organisms, but the highest BCFs occur in phytoplankton and algal species. In determining whether high BCFs in a certain group of organisms are indicative of increased hazard, it seems logical to consider whether there is reason to believe a pathway exists between the organisms showing high bioaccumulation and those having sensitivity to chemical exposure. In the case of lead, some algae are used by humans for food; this then suggests that high BCFs for algae do indicate the potential for increased hazard to humans and are therefore relevant to hazard ranking. A pathway to humans also exists through incorporation of algae into a food chain leading to another organism ingested by humans. In this instance, it is legitimate to consider whether this tropic transfer could result in exposure comparable to that associated with high BCF values. For lead and many other cationic metals, there is suggestion that concentrations decline with increasing trophic level.

In the case of some other metals, toxicity of the metal to humans may be much lower compared to lead. For example, copper shows substantial bioconcentration factors (even at concentrations above nutritional sufficiency) in some organisms, but ingestion of contaminated organisms by humans is of much lower concern than for a metal such as lead. The best understood mechanism of copper toxicity to aquatic organisms is through disruption of ionoregulation at the respiratory surfaces (e.g., gills), which does not have a connection to bioaccumulation *per se.* The evidence as to the toxicity of dietary copper exposure within the aquatic food chain is mixed; it is clear that some degree of dietary uptake of copper occurs, but the evidence is unclear as to whether this poses a toxicity threat.

Assessing bioaccumulation hazard for non-human receptors is more complex. Essentially all organisms are subject to predation by other organisms, so the plausible dietary exposure always exists for some receptor. Unfortunately, it is not common to have extensive data on the potency of dietary exposure for causing toxicity for non-human receptors.

With respect to hazard ranking/assessment, questions have arisen whether or not bioaccumulation data for some species should be excluded (or disproportionately weighted) when classifying the hazards of metals according to their bioaccumulation potential. It has also been suggested that such hazard evaluations be made in the context of pre-defined exposure scenarios (e.g., human health, terrestrial and aquatic-dependent wildlife). In theory, this practice might facilitate refinement of data used to indicate hazard potential (e.g., toxicity, persistence, bioaccumulation, etc.) to align with the constraints of the exposure scenario and protection goal. However, this benefit would come at the cost of additional effort expended to define and implement such additional analyses compared to the current hazard assessment approach.

> **Issue Summary No. 2.3.4:** For a given chemical, bioaccumulation data may be available from a number of different species (algae, zooplankton, macroinvertebrates, fish). For some regulatory applications, data from certain species (and tissue types) are preferred or excluded from consideration because protection goals are narrowly defined. For assessing hazard using the PBT framework under the TRI program, bioaccumulation data for each species are given equal consideration due in part to the broad assessment goals of the program (e.g., ranking hazard relative to all ecological and human receptors). **When classifying the hazards of metals according to their bioaccumulation potential, should bioaccumulation data for some species be excluded (or disproportionately weighted)? If so, which species should be weighted differently? Should metals hazard evaluations be made in the context of predefined exposure scenarios (e.g., human health, terrestrial and aquatic-dependent wildlife) in an effort to reduce uncertainty associated with combining independent indicators of hazard potential (e.g., toxicity, persistence, bioaccumulation, etc.)?**

Issue #5. Interdependence of Bioaccumulation and Toxicity in Characterizing Metal Hazard

As discussed above and elsewhere in this document, consideration of the bioaccumulative and toxic properties of a metal are among the important factors that need to be considered when evaluating or ranking the hazard of the metal. There may be situations in which the organism of concern (i.e., the organism to which the metal is toxic) also bioaccumulates the metal. In such situations it may be possible that the bioaccumulative properties of the metal in the organism are represented in the metal's toxicity to the organism. That is, the toxicity will only occur if the organism first bioaccumulates the metal. (This may be most likely if the adversely affected tissue is the same tissue in which the bioaccumulation has occurred; the bioaccumulation eventually leads to a tissue concentration sufficient to cause toxicity.) In situations such as this, what is the appropriateness of considering the bioaccumulation in making decisions regarding the bioaccumulative properties of the metal?

There may be situations in which the organism of concern also bioaccumulates the metal, and the bioaccumulative properties of the metal in the organism are **not** represented in the metal's toxicity to the organism. That is, the toxicity of the metal to the organism is not dependent upon or require prior bioaccumulation of the metal by the organism: they are independent phenomena. In this situation, criteria based on toxicity might be inherently underprotective, and it might then be appropriate to consider as part of the hazard evaluation or hazard ranking of the metal the bioaccumulative properties of the metal in the organism, in addition to the toxicity of the metal to the organism. Lead is an example of a metal that is toxic to humans and bioaccumulates in humans. Specifically, lead causes neurotoxicity and kidney toxicity to humans, and lead bioaccumulates in the human skeleton. Neither the neurotoxicity or kidney toxicity caused by lead requires prior bioaccumulation of lead in the human skeleton. Lead that has accumulated in skeletal tissue can, however, serve as an endogenous source of exposure to lead during periods of bone loss. It is well documented that under such physiological conditions lead that has accumulated in the human skeletal tissue can remobilize from the skeleton and enter other tissues. Consequently, if such exposure had not been considered in setting the toxicity criteria, either the additional hazard could be considered by accounting for such bioaccumulation independent of toxicity, or the toxicity criteria could be made more stringent to account for the additional exposure during periods of bone loss.

> **Issue Summary No. 2.3.5: In situations in which the metal under review causes toxicity to a certain organism (i.e., the target organism) and the metal also bioaccumulates in the organism, should bioaccumulation be considered independently of toxicity, and if so, what are the important factors that need to be considered regarding the use of these data for hazard identification or hazard ranking purposes?**

2.4 Persistence

Persistence refers generally to the ability of a material to remain in the environment. With respect to organic chemicals, it is generally characterized by the rate at which a chemical is broken down in the environment (e.g., by bacterial degradation or photo oxidation) into smaller compounds which are typically less hazardous than the original compound. For example, DDT (along with DDE and DDD) is generally considered as being persistent, because it is broken down to less toxic compounds very, very slowly (years and beyond). In contrast, the herbicide glyphosate is typically broken down to innocuous materials relatively quickly (days). The concept of persistence becomes more complicated when viewed in terms of metals. When metals are viewed as elements, they are infinitely persistent; copper atoms are never changed to any other atom under environmental conditions, but the speciation of the copper atom can change. The "persistence" of a particular metal species may, however, be very low under certain conditions (e.g., transformation of *aquo* Cu^{2+} to solid CuS in the presence of sulfide), which is not to say that it might not be transformed back to the original form when environmental conditions change.

These two approaches to defining persistence (persistence of a metal atom versus persistence of a physical/chemical form) are different in important ways, and discussions about "persistence" of metals must be carefully framed. Alternative definitions have been offered, e.g.,: "Persistence is a characteristic of a metal that is indicative of the constancy and duration of exposure of the available metal forms in a particular medium." (DiToro et al., 2001). This definition of persistence reflects the need to relate the exposure concentration to the potential for adverse effects and leads to consideration of a metal's rate and extent of transformation, it's complexation capacity, and the bioavailability of the dominant species as discrimination tools to allow one to make differentiations among metals and metal compounds. Proponents of this definition argue that, without specifying the compound of concern and where it is of concern, the concept of persistence has little meaning in the case of metals. In fact, for aquatic organisms the argument is made that, for metals and metal compounds that are insoluble and therefore relatively persistent, their persistency is a protective characteristic leading to less risk since toxicity is a function of a metal's free ion concentration.

Current Agency Practices

Persistence is generally not considered as a separate factor when conducting typical site-specific or national risk assessments. Instead, whatever information the risk assessor has on environmental fate is applied within the risk assessment models to ultimately predict exposure. For example, EPA has done extensive analyses of metals partitioning in soils and groundwater to allow modeling of the impact of metals leaching from wastes or contaminated soils into potential drinking water aquifers. The exception to this detailed analytical approach is in prioritization or ranking analyses where persistence is used as one of the surrogates for exposure. In these situations metals are generally considered infinitely persistent, while persistence for organic chemicals is generally expressed in terms of their half life in different environmental media.

> **Issue Summary No. 2.4.1:** While metals are infinitely persistent as elements, the "persistence" of specific metal compounds can vary with environmental conditions. **What approaches can be used to determine when and how persistence should or should not be considered when conducting a prioritization analysis? Is there an alternative way to define persistence of metals and/or metal compounds that could be used in national prioritization analyses that are designed to distinguish between metals?**

2.5 Toxicity

Toxicity is the *potential* of a substance to cause harm. Toxicity is commonly described in terms of hazard identification and dose-response. Hazard identification is the review of relevant toxicologic, biological, and chemical information to determine the nature and potential to induce adverse health effects. Dose-response associates health effects with a specified dose or exposure level. Toxicity is the link between dose and response, which equates to dose (exposure) with response (risk). The dominance of dose is often expressed emphatically as "The dose makes the poison" (paraphrased from Paracelsus [1493-1541] in Klaassen, 2001). Many regulatory and public health actions are designed to assure that exposures to humans and the environment will be at, or below, a given dose (or exposure) level in order to minimize the risk of adverse effects.

Essentiality

Several metals are essential for maintaining good health. Low levels of any essential metal can cause a nutritional deficiency that can lead to poor health, but high levels are toxic. The essentiality and toxicity of these metals pose unique challenges to their assessment and regulation in the environment. Essential metals with potential for toxicity at excessive doses include cobalt, copper, iron, magnesium, manganese, molybdenum, selenium, and zinc (Klaassen, 2001). As commonly occurring natural elements, the metabolism of metals has played a role in evolutionary development. The metabolism of an essential element, such as calcium, can affect the metabolism of a non-essential toxic metal, such as lead (Kern et al., 2000).

Speciation

As a defining characteristic of a metal, speciation controls toxicity, although some generalizations can be made across metal compounds based on valence, solubility, and covalent bonding with carbon and other elements. The valence state of a metal can modify toxicity. For example, hexavalent chromium is a potent known human carcinogen by the inhalation route of exposure, whereas trivalent chromium is much less toxic, not considered a carcinogen, and is an essential nutrient for humans. For other metals, solubility may act a surrogate for bioavailability, and can modify risk by limiting the biologically relevant dose. For example, insoluble nickel compounds (e.g., nickel subsulfide, nickel oxide) are carcinogenic when inhaled, but soluble nickel forms (nickel sulfate, nickel chloride) do not appear to be carcinogenic. Soluble forms of lead and arsenic are generally assumed to be more bioavailable than insoluble forms. The toxicity, mode of action, and exposure potential of organic mercury (methylmercury and dimethylmercury) differs from inorganic mercury (e.g., elemental or mercuric chloride). The fatality of a researcher handling dimethylmercury has underscored its extreme toxicity (Siegler et al., 1999) relative to other forms of mercury. On a national scale, combustion of organic tetraethyl lead proved to be an excellent predictor of blood lead levels (National Research Council Committee on

Measuring Lead in Critical Populations, 1993). Organic tin compounds are generally more bioavailable than inorganic forms (Klaassen, 2001). Speciation may also modify essentiality. For example, trivalent chromium is required for glucose metabolism, but hexavalent chromium is not (Klaassen, 2001).

Metabolism and Mode of Action

The metabolism and mode of toxic action for metals may be quite different than for organic pollutants. Metals adversely impact a wider array of target tissues. 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 (Shumilla et al., 1998). For example, chromium, cadmium, mercury, zinc, and arsenite inhibit thiol binding proteins. 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. Metabolism of the toxic metal may be similar to that of a related essential element (e.g. lead and calcium in the CNS; lead, iron, and zinc in heme metabolism). 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) (Kern et al., 2000). 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. For example, lead stored in the bones of a woman may be released during nursing, thus becoming an exposure and health issue for the nursing infant (Gulson et al., 2001).

Current Agency Practice

The Agency uses toxicity data to assess the hazards and risks of chemicals released in the environment. Toxicity assessments and values for metals occur within the same data bases as those for other compounds. The primary data base for human health toxicity values is IRIS (http://www.epa.gov/iriswebp/iris/index.html). The diversity of ecological receptors relative to the state of toxicological data means that ecological toxicity values are less standardized and are often developed on a site-specific basis using newly-generated data or data gathered from peer-reviewed literature. For non-cancer health effects, estimated doses (or exposures) are compared to reference doses (RfDs), reference concentrations (RfCs), or similar benchmarks to determine whether adverse effects are likely. Cancer risks are described as incremental increases in the probability of contracting cancer (cancer risks are usually assessed for human populations) per unit of exposure (or dose). Adverse ecological effects are evaluated at the population level rather than the individual level, unless the organism is a threatened, endangered, or otherwise protected species.

One major challenge is that emissions (and exposure data) for metals are typically reported as a total elemental metal (e.g., arsenic emissions) or as a compound class (e.g., arsenic and arsenic compounds). Occasionally, emissions data include some limited information about the metal forms (e.g. sulfides of nickel). Emissions data are rarely available on specific species (e.g., nickel subsulfide). This lack of data on specific species can be problematic for the risk assessment. Risk assessors are often faced with making simplified assumptions when comparing exposure estimates with toxicity data that are not concordant for the species (or route of exposure). For example, the inhalation toxicity data for nickel subsulfide are quite good, but the data for nickel oxide are limited. Likewise, substantial data exist on effects of methylmercury, but data on dimethylmercury are more limited.

The selection of these assumptions and defaults should be based on good scientific judgement, and should be as consistent between the exposure and toxicity data as possible. In general, the data needs and the importance of considering these issues will depend on how refined an assessment is needed and the relative significance of the decision. For example, refined assessments being utilized to set costly regulatory levels will require solid analyses and robust data, but a relative ranking analysis to determine priorities, may have more modest needs.

> **Issue Summary No. 2.5.1:** As described in previous sections, at issue is whether the toxicity data and dose-response values for metals are adequate when metals are known to occur as distinct compounds or species which can transform dynamically (both spatially and temporally) in response to controlling environmental conditions. **What data gaps do you consider to be the key limiting factors to performing robust hazard and risk assessments? What methods could be used to account for limitations in the existence of compound-specific toxicity values when assessing metals-related hazard/risk?**
>
> **Issue Summary No. 2.5.2:** Related to the adequacy of the toxicity data base, is the availability of parallel sampling and analytical methods to collect, identify, and quantify the relevant metal species in the environment. Parallel analytical methods are needed for consistent and scientifically sound assessments to link toxicity data with environmental concentrations of the relevant metal species. A similar set of analytical questions follows from examination of the adequacy of the toxicity data base. **What are the limitations of current analytical methods to measure metal speciation in the environment? Which toxicity and exposure issues create demands for new analytical methods?**
>
> **Issue Summary No. 2.5.3:** Understanding the biological significance of metals in the environment often requires considering essentiality as well as exposure levels that cause toxic effects. Essentiality should be considered in the development and application of toxic dose-response reference levels such as reference doses (RfDs) and reference concentrations (RfCs). For example, appropriate uncertainty factors or modifying factors should be used such that an RfD is not lower than the recommended intake level for adequate nutrition. **Should existing risk assessment methods be modified to account for essentiality? If so, what options should be considered?**

3. Description of the Framework

The Framework will be patterned after the Agency's Ecological Risk Assessment Framework (EPA/630/R-92/001; February, 1992). The Framework will lay out key scientific principles and issues that need to be addressed in assessing metals; develop conceptual models for different scenarios and types of environmental decisions; and identify the kinds of scientific information, approaches, methods, and models that are available for differentiating among metals as to their human health and ecological risk. The following is a proposed outline of the Framework:

Outline of the Framework for Assessing Hazards and Risks of Metals and Metal Compounds

1. Introduction

1.1. Purpose and Scope of this Framework

1.1.1. Purpose and audience
The document will develop a cross-Agency framework describing basic principles that need to be considered in assessing the hazards and risks posed by metals and it will present a consistent approach for making these assessments. The audience of the framework is primarily risk assessors and the document will also communicate principles of metal assessment to stakeholders and the public.
1.1.2. Scope
The framework is a science-based document that focuses on the special attributes and behavior of metals and metal compounds affecting hazard and risk. It will supplement existing guidance and discuss key issues with metal-specific information. The approach will include metal-by-metal considerations and it will vary depending on level of scientific assessment needed and scope of regulatory activity.
1.1.3. Tiered Approach
A tiered approach will be developed which, as an initial approach, incorporates the regulatory context of the assessment. The initial tier where the least amount of metal and metal compound-specific information would likely be used would occur in National Hazard/Risk Ranking and Characterization. An intermediate tier would include National Regulatory Assessments which set media standards or guidelines for chemicals. The third tier, addressing primarily Site-Specific Assessments, would incorporate metal and metal compound-specific data and environmental chemistry information to a greater degree due to the nature of these assessments.

1.2. Overview of Key Issues.
An overview of key issues that expands upon what is discussed in section 2 of the Action Plan.

1. Appropriate application of chemical speciation data to assessments,
2. Addressing bioavailability in the assessments of metals,
3. Evaluating bioaccumulation in relation to metals,
4. Persistence as it relates to metals and metal compounds, and
5. Metal toxicity issues as affected by speciation, bioavailability, and routes of exposure.

2.0 Problem Formulation and Scope of the Analysis

Problem formulation is defined by considering laws and policies that apply to the sources of metals and metal compounds, the nature of the problem, and the likely scale of the assessment (both temporal and spatial). The goal of planning is to identify the context of the environmental decision, the risk management objectives, the options under assessment, the type and level of analysis needed, and available resources, and to resolve questions concerning scope and process.

2.1 Regulatory Context

This section describes three general groupings of regulatory actions where the metal issues may arise.
2.1.1 National Hazard/Risk Ranking and Characterization. These are used to set priorities or rank chemicals in regulatory activities or activities such as voluntary pollution reduction efforts.
2.1.2. National Regulatory Assessments. These assessments are done when the Agency is setting media standards or guidelines for chemicals.
2.1.3. Site-Specific Assessments. The environmental setting for the analysis is clearly defined and the analysis is focused on evaluating data appropriate for that setting.

2.2 Metal Exposure Pathways and Ecosystem(s) Potentially at Risk

Issues to consider include: routes of exposure to be evaluated in the assessment or regulatory action; metals and metal compounds; available information and data gaps; and pathways of exposure to ecological systems.

2.3 Mechanisms of Toxicity and Hazard Identification

This section will address the unique aspects of the toxicity of metal compounds to humans and ecological endpoints. Within the regulatory context under consideration, methods to address data availability will be presented.

2.4 Assessment Endpoint Selection

Processes will be presented to select the human health or ecological components to be protected. Principles to determine sensitive subpopulations that receive significant exposure to the chemical of concern will be developed.

2.5 Conceptual Models

The conceptual model shows the interrelationship between the metals and metal compounds and the assessment endpoints. Endpoints are selected for their relevance to management goals, societal values and laws, known adverse effects of metals, and the endpoint importance to stakeholders. The model depicts the pathways from sources of metals to receptors and environmental processes, fate and transport routes which affect the types of metal compounds and exposures that may occur. Conceptual models are case specific and in this framework we will consider three categories: national hazard/risk ranking and characterization, national regulatory assessments, and site-specific assessments.

3.0 Analysis Phase

3.1 Characterization of Exposure

3.1.1 Exposure pathway analysis. This section addresses the evaluation of the significant exposure pathways and routes of exposure to the human health or ecological endpoints to be protected, e.g. inhalation, ingestion, etc.
3.1.2 Metal speciation and distribution. Level of specification will depend on tier or regulatory context. The development of principles to discuss metal speciation on a metal and metal compound basis will be considered in this section. The identification of prevalent metal forms in the environment will support the discussion.
3.1.3 Ecosystem(s) characterization. In the appropriate tiers or regulatory context, the development and application of methods to evaluate the impact of ecosystem physical, chemical, and biological parameters on the transport, transformation, and availability (or speciation) of metals is important in the assessment of metals. Assess methods to incorporate natural background levels of metals and consider adaptation/acclimation issues in wildlife.
3.1.4 Exposure distribution/ analysis. In the higher tiers, processes to estimate the concentration distribution of metals and metal compounds are needed. Approaches will be considered to address these issues.
3.1.5 Bioavailability. Discuss issues for addressing within organism bioavailability issues from the various routes of exposure in a tiered process. Approaches should be considered to further incorporate bioavailability issues into regulatory processes.

3.2 Characterization of Human Health Effects

Issues to consider include: assessing the routes of exposure that are of most concern; identifying the toxicological endpoints; utilization of a dose-response profile or a distribution that characterizes the effects of the metal on the endpoints of concern; methods to relate the primary toxic forms of the metal and metal compounds versus forms most common in the environment; and essentiality issues.

3.3 Characterization of Ecological Effects

Issues to consider include: metal toxicity and essentiality; processes for higher tiers to discuss metal compounds tested and likely forms of the metal in the environmental media of concern; evaluation and application of bioaccumulation methods; direct vs indirect toxicity; mobilization of stored metals;

processes in higher tiers to utilize models to relate aquatic and soil chemistry information to toxicity; depending on tier or regulatory context, application of dose-response profiles, species-toxicity distributions, or probabilistic assessments.

4.0 Characterization of Exposure and Effects

4.1 Integration of dose-response with exposure pathways

Depending on the tier and regulatory context, what processes should be considered to assess the hazard or risk assessed from major pathways of exposure (e.g., inhalation, ingestion, etc.)? Discuss approaches to address bioavailability issues in a tiered process. What principles should be applied to metal complexation/precipitation issues from physical and chemical characteristics of the environmental media (water, soil, sediment)?
For a given regulatory tier, what processes should be used to assess sensitive human and ecological endpoints? Discuss processes or calculations that should be used to determine sub-populations most at risk

4.2 Weight of Evidence

What levels of detail (tiers) are available for the evaluation of each aspect of hazard and risk? How can background concentrations and weathering of metals be addressed? What approaches should be used to evaluate metal speciation in the toxicity data base versus speciation of metals in the exposure pathways? Are special data requirements needed for evaluating particular metals and metal compounds?

4.3 Uncertainty Analysis

What tiered process would be appropriate to evaluate uncertainty around risk estimates? When should sensitivity analyses be applied? How should relating the value of additional information versus cost be considered?

4.4 Case Studies.

For each regulatory tier, case studies should be developed to provide examples of how scientific data on metals can be utilized in the assessment process. How does the nature of the management decision presented in the case studies change the application of metal environmental chemistry?

5.0 Regulatory Applications and Implementation of the Framework

Discuss and compare practices among the statutes for assessing hazards and risks of metals and metal compounds. Identify examples of the different tiers from statutes, regulatory guidance and criteria for risk management. Discuss the handling of tiered approaches for addressing issues, information needs, and research recommendations.

6.0 Research to Reduce Uncertainty

Within the tiered structure, discuss what research is required to enable assessors to apply increased levels of metal-specific data on environmental chemistry, models, exposure and effects analysis, and characterization. What process can be used to prioritize research topics that can reduce uncertainty in metal assessments? What methods can effectively promote partnerships with the academic community and Federal agencies to coordinate research to address high priority topics?

– End of proposed outline –

4. Description of the Guidance for Characterization and Ranking of Metals

Whereas the Framework will consider issues and principles applicable across EPA's regulatory activities, the Agency recognizes the need to take the next essential step of providing cross-Agency guidance for applying these principles. The Guidance for Characterizing and Ranking Metals will provide the tools and specific guidance for characterizing metals and assessing hazard and risk, and it will address critical needs identified by the stakeholders.

Risk prioritization and ranking exercises typically involve relatively rapid evaluation and comparison across a significant number of chemicals, either in a single media or across media. The purpose of these exercises is generally to identify those chemicals which have a greater potential to cause harm in the environment by looking at available indicators which are good predictors of hazard and risk. The predictors which have been used by a number of Agency programs are persistence, bioaccumulation potential, and toxicity. Chemicals having these properties are of particular concern because they remain in the environment for long periods of time, accumulate in organisms, can be transferred to other organisms within the food web, and may cause a range of serious toxic effects such as neurological disorders, reproductive and developmental problems, genetic damage, and cancer. In recent years there have been increasing concerns both nationally and internationally over the hazards and risks posed by persistent, bioaccumulative and toxic substances (PBTs). Over the years, PBT chemicals have gained a great deal of public attention and concern due to the public health and environmental problems they have caused. Many PBT chemicals are included in international agreements directed at reduction or elimination of hazardous PBT pollutants.

There appears to be consensus among a number of organizations as to how to evaluate the persistence, bioaccumulative, and toxicity of organic chemicals; however, such a consensus has not been reached in the case of metals because of the various issues described earlier in this plan. The controversy surrounding the recent decision (Lead and Lead Compounds; Lowering of Reporting Thresholds; Community Right-to-Know Toxic Chemical Release Reporting; Final Rule. 66 Federal Register, 4499-4547 (January 17, 2001) by the Agency that lead and lead compounds are PBTs underscores the importance of developing guidance specific to metals that can be applied for purposes of classification and priority setting.

The Guidance for Characterization and Ranking of Metals developed from this Action Plan will build on the principles laid out in the Framework and will focus on how these principles and available methods can be applied in a hazard ranking/characterization context. It will also take into consideration on-going activities outside the Agency.

5. Overall Approach and Schedule for Development of the Framework and Guidance

This Action Plan will culminate in two guidance documents (the Framework and the Guidance for Characterization and Ranking of Metals). The Agency sees these activities occurring in parallel and being closely linked (see Figure 1). The Framework will provide the overarching principles and methods for metals assessment that can be applied across EPA's programs to assure consistency in addressing the various scientific issues described earlier. A peer consultation review of this draft document is projected for April 2003 followed by SAB review in June 2003. The Guidance for Characterization and Ranking of Metals will address the application of the principles and specific methods identified in the Framework to the issue of how to differentiate among metals and metal compounds for purposes of setting priorities and categorization. Activities that this Guidance will apply to include information gathering, testing, and the like. A peer consultation review of this draft document is projected for September 2003 with SAB review in November 2003. At the time that the Agency brings the Guidance for Characterization and Ranking of Metals to the SAB, it will also request the SAB to comment on whether lead is highly bioaccumulative, an issue which arose in the earlier TRI Lead rulemaking.

The Office of Research and Development will lead the effort to develop the Framework, the Office of Solid Waste and Emergency Response (OSWER) will lead the effort to develop the Ranking and Categorization Guidance, and EPA's Risk Assessment Forum will be charged with organizing the necessary peer involvement workshops and the development of white papers that will allow the Agency to tap into the body of outside experts and coordinate its activities with ongoing efforts nationally and internationally. A hallmark of this effort will be opportunities for peer involvement and peer review.

Development of White Papers

As a first step, the Agency will develop white papers on the major scientific issues and sub-issues described in this Action Plan. These white papers will summarize the state-of-the science of each assessment issue and identify available approaches, models, and extant data that can be applied to each of the three regulatory scenarios described earlier. The white papers will serve as a major information source for the Framework and Categorization and Ranking Guidance, and will help focus discussions at the first peer consultation workshop. An additional use of these white papers will be to help guide EPA's future research efforts in the area of metals assessment.

A model for development of these white papers is a process that was effective in developing the Agency's first Ecological Risk Assessment Framework. Teams consisting of EPA staff and outside experts will be formed around each specific issue to develop the white papers. This approach should facilitate consensus building and take advantage of related activities taking place outside the Agency.

Peer Consultation Workshops

The Plan includes three peer consultation workshops which will provide an opportunity for the scientific community and stakeholders to have input to the scope and direction of both the Framework and the Ranking and Categorization Guidance.

Workshop 1 will be held in November 2002. Input to the workshop will be the recommendations from the SAB Advisory on the Action Plan and the state-of-the science white papers. At the workshop, participants will refine the scope and content for both the Framework and the Ranking and Categorization Guidance based on the SAB's recommendations and the white papers. The intended outcome of this workshop is consensus as to the annotated outlines for both documents.

Workshop 2 is planned for April 2003 and will be an opportunity for the scientific community and stakeholders to provide input on the draft Framework. This workshop will be held sufficiently in advance of an SAB review of the Framework so that recommendations from the workshop can be considered for inclusion/modifications of the draft before it goes to the SAB for review.

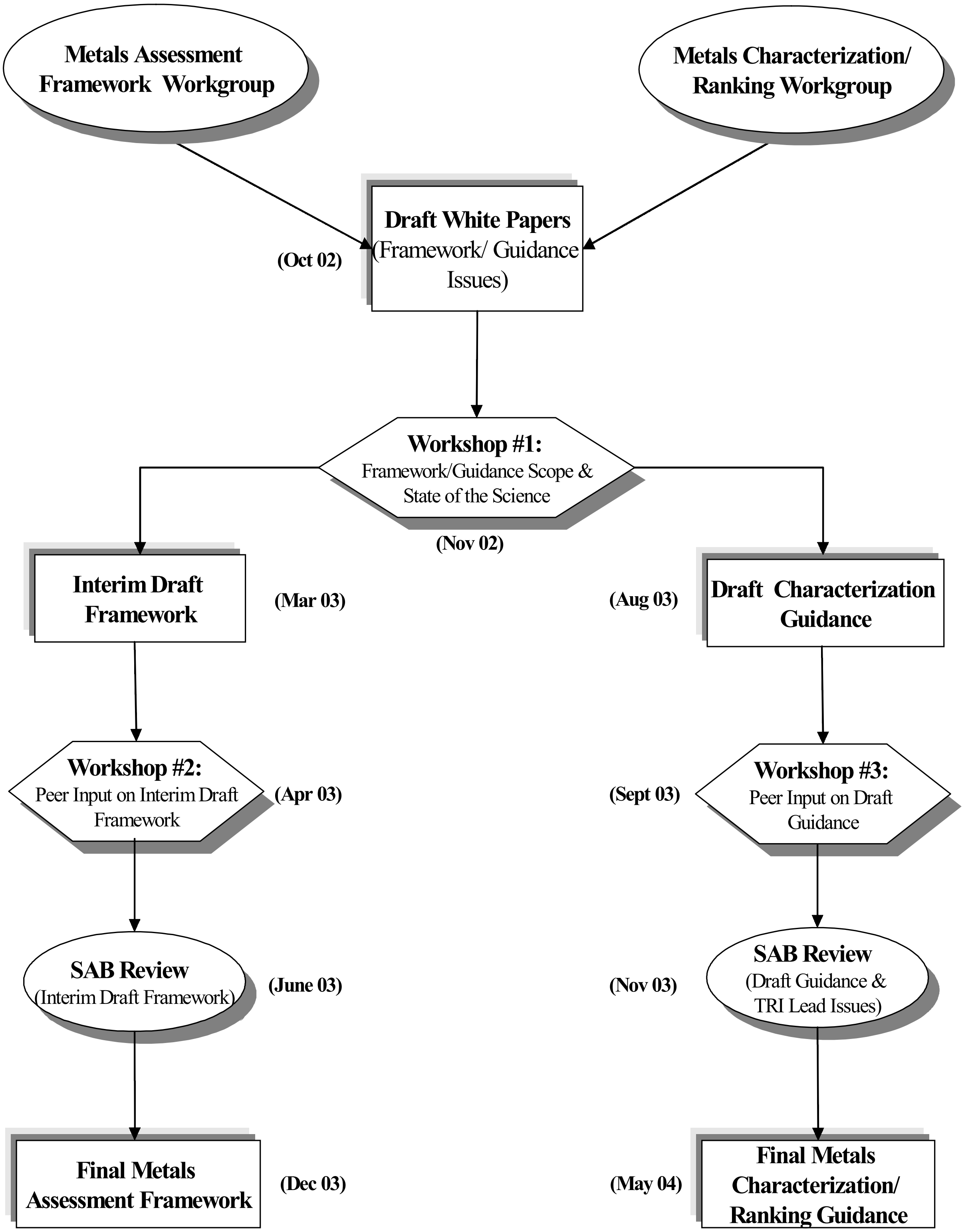
Workshop 3 is planned for September 2003 and will be similar in organization to *Workshop 2* but will focus on the draft Ranking and Categorization Guidance. This workshop should benefit from the June SAB review of the Framework. Recommendations coming out of this workshop will be considered for inclusion/modifications of the draft before it goes to the SAB for review in November 2003.

Science Advisory Board Review

In addition to the SAB Advisory on the Action Plan, two SAB reviews are anticipated. The first review planned for June 2003 will review the draft Framework. The SAB meeting will also provide another opportunity for public input. The second SAB review in November 2003 will focus on the Ranking and Categorization Guidance and include review of the outstanding issue from the TRI lead rulemaking as to whether lead can be considered to be highly bioaccumulative under the TRI criteria. This review will take place after the review of the Framework to allow for any needed adjustments based on the SAB's review of the Framework. Overall the Framework is planned for completion in December 2003 and the Ranking and Categorization Guidance within six months after completion of the Framework.

Figure 1 presents the overall process and schedule for the production of the Framework and Ranking and Categorization Guidance.

Figure 1. Development of Metals Assessment Framework and Metals Characterization/Ranking Guidance



6. Outreach Activities

In carrying out this Action Plan, the Agency will involve the following groups to foster consensus building:

The Scientific and Risk Assessment Communities

EPA will seek out opportunities to engage the scientific and risk assessment communities as it develops the Framework and the Guidance for Characterization and Ranking of Metals. The following examples are illustrative.

EPA staff are working jointly with scientists from academia, industry, and Environment Canada to organize a Technical Workshop under the auspices of the Society for Environmental Toxicology and Chemistry. The workshop is titled *Hazard Identification Approach for Metals and Inorganic Metal Substances* and has been proposed to the SETAC Board of Directors. The workshop will involve environmental regulatory agencies in North America and Europe, as well as industry, academicians, and environmental organizations. Since the intent of the workshop is to summarize the current state-of-the-knowledge and propose methodologies and criteria that may be useful for hazard assessment of metals and inorganic metal compounds in a regulatory context, we see direct relevance to our efforts. The information developed through this workshop will complement our white paper development and contribute to the consensus building process.

Another avenue that is being explored is discussions with the Center for the Study of Metals in the Environment. This is a consortium of eight universities funded by EPA that is addressing questions concerned with the risks of metals in the environment through research, technology transfer, outreach, and education. The Center is an outgrowth of a research consortium focused on Bioavailability, Trophic Transfer and Fate of Pollutants in the Aquatic Environment previously funded by EPA. Opportunities are being identified where complementary activities would be beneficial.

Coordination with Other Federal Agencies

The Agency will coordinate its activities with other interested agencies as it moves forward in developing the metals assessment guidance. For example, EPA staff are currently participating in an interagency effort to characterize and distill the data needs for assessing the risks from exposure to metals in various settings (e.g., occupational and environmental settings and considering issues of route and speciation of the metal form(s) to be tested). The interagency work group which is forming will work towards developing an overall strategy consisting of (1) identification of key testing needs, (2) development of testing approaches for efficiently and effectively meeting those needs, and (3) consideration of appropriate, available mechanisms for meeting specific data needs for metals risk assessment (including, for example, federal research, testing sponsored by the National Toxicology Program [NTP] or by industry (through voluntary efforts or by regulations under the Toxic Substances Control Act [TSCA]), etc.).

Communication with Stakeholders

EPA will take steps to ensure a broad range of stakeholders–including the regulated community, the environmental community, and the public in general–are kept informed of and invited to participate in the process. At the February 2002 workshop, stakeholders expressed a strong interest in being kept informed as EPA moves forward in developing the metals assessment guidance. One suggestion that is being pursued is a webpage (to be implemented within the Risk Assessment Forum's website) where stakeholders can be kept abreast of progress, upcoming workshops and reviews, and have access to external review drafts, i.e., white papers and guidance documents. The three peer involvement workshops and two SAB reviews are other opportunities for stakeholder input as the Agency moves forward.

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