Public Comments on the Draft SAB Metals RA Framework Report

1. Comments of the National Metals Council -- Dr. William Adams

October 31, 2005
VIA E-Mail: Miller.tom@epa.gov
Mr. Tom Miller
Designated Federal Officer
EPA Science Advisory Board
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Comments on SAB Draft Report (9/15/05) on EPA's Draft Framework for Inorganic Metals Risk Assessment

Dear Mr. Miller:

The North American Metals Council ("NAMC") appreciates the opportunity to provide comments on the September 15, 2005, Draft Report prepared by the Science Advisory Board ("SAB") on EPA's Draft Framework for Inorganic Metals Risk Assessment. The SAB's Draft Report will be considered at the SAB teleconference on November 7, 2005, see 70 Fed. Reg. 60338 (October 17, 2005). NAMC is an unincorporated group of 30 metals-producing and-using associations and companies that focuses on science and policy-based issues that affect metals in a generic way. Its members include representatives of a broad cross-section of metals industries that have a strong interest in the scientific issues that are presented in the draft Framework.

NAMC has been actively involved in the issues that are the subject of the ongoing SAB review and submitted written and oral comments to the SAB panel during its deliberations. Our comments consist of the points made directly below in the text of this letter, briefly addressing specific points raised by the SAB Draft Report, as follows:

SAB Draft Report

Executive Summary: *Use of the term "Bioaccumulation" versus "Accumulation" to Describe Metals Concentrations*….. "The SAB believes it important to recognize that some metals do bioaccumulate in the tissues of humans and that this bioaccumulation is related to their toxicity."

NAMC Comment:

The statement above does not clearly distinguish bioaccumulation and toxicity as separate concepts for assessment; nor does it reflect the fact that bioaccumulation/accumulation can occur in some organs without concomitant effects. If this point is retained, the emphasis should be changed from "bioaccumulation is related to toxicity" to "*toxicity is related to bioaccumulation*."

NAMC recommends the following clarifications:

- The above statement should be changed to read: "*The SAB believes it important to recognize that some metals do bioaccumulate in the tissues of humans and that toxicity may occur when effects thresholds at the site of action are exceeded*."

NAMC further notes that the SAB Draft Report as well as the EPA Draft Framework do not point out the absence of scientifically reviewed approaches for measuring or assessing the significance of bioaccumulation in humans. In the absence of such approaches, the use of bioaccumulation in humans to prioritize the need for further assessment or regulation of metals and other substances in commerce is problematic.

NAMC recommends the following change in the same section of the report:

- To the new sentence above we recommend adding: "*Scientifically recognized approaches for measuring or assessing the significance of bioaccumulation in humans have not been developed to date*." It would now read in its entirety, "The SAB believes it important to recognize that some metals do bioaccumulate in the tissues of humans and that toxicity may occur when effects thresholds at the site of action are exceeded. Scientifically recognized approaches for measuring or assessing the significance of bioaccumulation in humans have not been developed to date."

- Similar changes to the discussion in section 5, page 8 should also be included.

<u>SAB Draft Report</u>

Executive Summary: Definition of the term "Bioaccumulation." The Draft Report proposes to define this term (with the italicized portion as a proposed addition) as: "The net accumulation of a metal in a tissue of interest or the whole organism that results from exposure to all environmental sources, including air, water, solid phases (i.e., soil, sediment) and diet, *and that represents a net mass balance between uptake and elimination of the metal*."

<u>NAMC Comment:</u>

The phrase "net mass balance between uptake and elimination of the metal" is potentially confusing. The intent of the proposed definition appears to be focused on an <u>increase</u> in the steady-state body burden of a metal as a result of uptake exceeding elimination of the metal. The phrase "net mass balance" conveys equilibrium rather than an increase. NAMC recommends that the SAB revise this definition to express more clearly what is intended -- or delete it.

<u>SAB Draft Report</u>

Section 5, page 5 now reads: "The discussion of simultaneously extracted metals – acid volatile sulfides (SEM-AVS) does not adequately address the limitations of the approach (e.g., bioavailability from oxidized sediments). Similarly, discussions of the biotic ligand model (BLM) do not adequately describe its limitations or the early stage of BLM development. Finally, other approaches such as the National Oceanic and Atmospheric

Administration's (NOAA) empirically-derived effects range median (ERM) and effects range low (ERL) approach (Long & Morgan, 1990; 1991) should be included in the discussions."

NAMC Comment:

NAMC agrees that the Framework should address limitations of the SEM-AVS approach, especially its application to oxidized sediments. At the same time, it is important to note that extensive research has been supported by the metals industry on copper, zinc and nickel the past three years to address this issue with more than 200 chronic sediment toxicity tests being performed. This work is making its way into the peer reviewed literature. The intent has been to develop a basis for assessing bioavailability of metals in oxidized sediments as well as anaerobic sediments where sulfide chemistry dominates.

NAMC has serious reservations about recommending the approach of Long and Morgan as an overarching recommendation to EPA. The methodology of Long and Morgan is not metals-specific, does not consider bioavailability and cannot ascribe effects to a given substance. We believe the Agency should be encouraged to develop metal-specific methods for sediment assessment. Approaches such as that of Long and Morgan may have utility as an interim approach for national assessments, but their significant limitations should be noted.

NAMC recommends the following change to the above sentence:

- "The discussion of simultaneously extracted metals – acid volatile sulfides (SEM-AVS) does not adequately address the limitations of the approach (e.g., bioavailability from oxidized sediments). Similarly, discussions of the biotic ligand model (BLM) do not adequately describe its limitations or the early stage of BLM development. Finally, *other approaches based on empirically-derived effects thresholds, with their strengths and limitations, should be included* in the discussions."

SAB Draft Report

Section 6.3.14.1, page 72, now reads: "The BLM is in the relatively early stages of development and also has inherent limits. For example, the BLM: 1) has no dietary component; 2) has no chronic component; and 3) has no cross-species comparisons among differing mechanisms for binding and effects-level metal concentrations."

NAMC Comment:

To assist with the accuracy of the SAB review, NAMC points out that chronic BLMs have been developed and published for zinc and copper for algae (*Selenastrum* sp.), fathead minnows and *Daphnia magna*. The model is nearing completion for the same species for nickel and is under development for cadmium, silver, aluminum and cobalt. Since the development of this approach in the early 1990s the BLM has advanced significantly and characterizing it as in early development is not entirely accurate. It is true that a dietary component has not been built into the approach, but cross-species comparisons with differing mechanisms have been done and continue to be done.

Further, chronic BLMs exist as noted above. (Literature citations for the above referenced chronic BLMs can be provided.) We recommend that the statement in section 6.3.14.1 be revised to reflect these points.

SAB Draft Report

Section 6.3.14.1, page 73 now reads: "For risk assessments of a broader nature, e.g., at the national level, clearly the only viable approach to be implemented may be through the assessment of bulk sediment numbers."

NAMC Comment

It is recommended that the above recommendation be modified to reflect the developing state of the science. National risk assessments have recently been completed in Europe for zinc, copper and nickel. These are the most comprehensive assessments for metals to date and, to a large degree, they have not relied upon the use of bulk sediment numbers. Rather, specific approaches have been used for oxidized and non-oxidized sediments where bioavailability has been considered; bulk numbers are used only as a first tier screening level assessment. We point out that bulk sediment assessment is one way of performing national assessments.

Thank you for the opportunity to submit comments on the SAB Draft Report on EPA's Draft Framework, which NAMC believes will place EPA's assessment of metal-related hazards and risks on sound scientific footing.

Sincerely,

William J. Adams, Ph.D.
Chairman, NAMC

2. U.S. Department of Energy -- Ms. Debra Littleton

Staff Comments
On the Environmental Protection Agency (EPA) Science Advisory Board (SAB)

Draft Report to Assist Meeting Deliberations (9/15/05)

Review of EPA's Draft Framework for Inorganic Metals Risk Assessment

U.S. Department of Energy, Office of Fossil Energy, Office of Planning and Environment

DOE staff has been extensively involved with the EPA Metals Risk Assessment Framework during the last several years and believe the document is well done. DOE is very interested in continuing to work with the EPA regarding revisions that would be made prior to finalizing the Framework. In reviewing the draft SAB Review Panel report, DOE agrees with a number of comments but finds many others that could introduce confusion to the EPA Framework revision process. The following points include selected examples of where clarification would be helpful, with the aim of guiding an effective revision effort to limit potential misinterpretation by the risk practitioners who will ultimately apply this very useful Framework.

General Comments

1. Extensive revision requests

The draft SAB report represents a broad review effort and provides helpful information across many charge questions. However, DOE disagrees with the SAB Panel's statements that substantial revisions are needed to the Framework, which is a strong document that contains a great deal of sound scientific information and significantly advances the state of the practice for joint ecological and human assessment of inorganic metals. A number of SAB Panel comments and recommendations of particular interest/concern to DOE are discussed within specific comments below – including those related to bioconcentration factors/ bioaccumulation factors (BCFs/BAFs), bioavailability, bioaccumulation and toxicity.

2. Definitional inconsistencies

DOE notes a number of terminology issues that make suggested Framework revisions unclear. Wording preferences such as the use of principles vs. factors are not a key issue (see comments on *page 15, lines 13-14*, and later SAB use, e.g., *page 44, line 40*); rather, the concern is consistency in how technical terms are used in the Framework compared with other scientific documents. For example, the Panel seems to confuse distribution (pharmacokinetic processes) with toxicity (pharmacodynamic processes), bioaccessibility is referred to as bioavailability, and the reference dose or concentration (RfD/RfC) is incorrectly represented as an increment to a body burden. The DOE encourages the Panel to revisit its terminology and interpretation for consistency with scientific risk assessment practice, keeping in mind the Framework's target audience.

3. Scope inconsistencies

DOE understands the Framework's objective to be to outline scientific principles and consistent approaches for conducting metals risk assessments, focusing on inorganic metals.
DOE believes the Agency has effectively identified basic concepts, principles, and methodologies with useful illustrations to highlight key points, as appropriate for a framework. In contrast, many Panel comments seem inconsistent with this scope, requesting less detail in useful areas and more detail on several topics that are beyond a framing scope. To illustrate, the requested evaluation of the benchmark dose (BMD) modeling and no observed adverse effect levels (NOAELs) *(page 41, bullet 5)* would be appropriate for other programs (e.g., the EPA Office of Research and Development's Integrated Risk Information System), not the Framework. A similar issue applies to what seems an overstatement (considering that diet is a major exposure route), "… nanoparticles are now of critical concern for the exposure and delivery of metals to humans" *(page 25, lines 20-21).* Many requested additions appear to address such emerging areas or developmental tools for which the state of the science and practice has not yet advanced to the level sufficient for useful discussions in a Framework that is designed to guide practical applications.

At the same time, the Panel asks EPA to remove good information. For example, regarding the section on Metals Research Needs, the Panel states, "There has not been a thorough review of all research areas and it is not appropriate in the given context to highlight and identify specific research needs for the future" *(e.g., page xv, last bullet, and end of page 12-top of page 13).* DOE considers this section valuable and strongly encourages that it be retained. It captures issues gleaned during the Agency's preparation of the Framework and provides insights into next steps in this important area, as a research bridge for gaps identified in the Framework, the supporting issue papers, and further review inputs. As such, this section embodies the inclusive approach EPA took in developing the document. Furthermore, DOE notes that this section does not claim to be a comprehensive review of all possible areas, but rather offers useful content across integrated research needs from various contributors. Whether its non-inclusive nature is further emphasized in the introductory text or this is moved to an appendix, DOE endorses retaining the section for many interested users who would find it much more difficult to locate in a separate document, where the integrated context would be lost (and for which joint timing could be an issue).

As a note, the Panel seems to request various discussions without acknowledging material already provided in the Framework (from tools to concepts such as mimicry and organic-metal interactions). Also, in some cases references are requested that either do not reflect scientific consensus or have already been accounted for in the Framework. (For example, the NAS reference requested at the *top of page 21* is included in the Framework, and a more recent study on that topic is included as well. Regarding the 17-year old mixtures citation at the *top of page 29*, the Framework includes much more recent references such as EPA 2000 that improve on that early report.)

4. <u>Recommendation inconsistencies</u>

Certain comments regarding EPA recommendations appear inconsistent in terms of tiering or phrasing. On the first issue, the Panel asks EPA to tier its recommendations "with the most critical (those with the greatest impact) presented first" *(page 7, lines 6-7)*, while elsewhere *(page x, line 7)* the direction appears to be to order the recommendations by specificity (not importance), from general overarching to more specific. It would be helpful if the SAB Panel would clarify what organization is being requested, and if it is to be based on importance it would be useful to identify how the greatest impact would be defined (considering human and ecological applications at multiple scales, likely involving multiple preferences).

With regard to phrasing, the Panel asks EPA to express its recommendations as such *(page x)* but then requests wording be changed from recommended to "considered" *(bottom of page 26 to top of page 27)* and advises against recommending a particular model or approach *(page 23, bullet 1).* Given that EPA's Framework is to be a practical resource for risk assessors, and that current recommendations regarding available tools clearly contribute to that purpose, it would be helpful for the Panel to reconcile its recommendation comments.

<u>Specific Comments</u>

1. BCF/BAF

The SAB Panel states *(page xiii, 1st bullet)* "The SAB agrees … that BCF/BAF methodologies are not good measures of hazard for metals. However, the SAB finds that a clearer more systematic discussion is needed in the document to justify this statement. …include a discussion of what could replace BCF/BAF as a measure of bioaccumulative potential, and where BCF/BAF approaches are useful." DOE agrees with the Panel that BCF/BAFs should not be used in hazard ranking or national-scale assessments, and agrees that a discussion on how to use them in site-specific situations would be useful. To be clear on this issue, the SAB Panel and EPA should directly state that BCFs/BAFs do not apply for humans.

2. Bioaccumulation

The definition proposed by the SAB Panel does not reflect distinctions between human and ecological risk assessment practice. As a scientific or academic principle, DOE agrees with harmonizing terms. However, this Framework is to guide practical risk assessments across disciplines so it is important to consider whether a lumped definition loses its practical benefit to the applications for which it was developed (ecological assessments) while confusing those to which it is being extended (human health assessments). DOE believes using the general term "accumulation" instead of bioaccumulation for the human health context could reduce confusion associated with changing established definitions in use across various programs.

DOE notes that using separate definitions is supported by substantial Agency precedent for ecological and health risk assessments, simply reflecting differences in the processes, data, and state of practice for each field. Although many (not all) underlying principles are common, the scientific community of risk assessors has relied on established distinctions in key definitions to guide appropriate analyses. For example, trophic transfer is a common element of bioaccumulation definitions, and terms like critical body residues are used because many ecological measurements are whole-body data. In contrast, health assessment guidance does not include this definition, referring instead to accumulated tissue concentrations (whole body data are not relevant) with an emphasis on the target organ/system or site of toxic action. Also, terms such as mode and mechanism of toxic action, target organ toxicity dose, point of departure, margin of exposure, and toxicologic interaction, have been defined specifically for health assessments (see the EPA 2000 Mixtures Guidance).

Furthermore, in ecological assessments, bioaccumulation typically represents steady-state (equilibrium) conditions, while for humans, distribution and intermediate redistribution within a metal's biological retention time can be very dynamic, with potential accumulation or sequestration affected by factors such as lifestyle and nutritional status. Thus, for human assessments, a given measure of accumulation reflects the recent exposure profile as a temporal snapshot, which is much different from how bioaccumulation is used for ecological assessments. Such important distinctions are inadequately addressed by the proposed combined definition of bioaccumulation, and that should either be revised or rephrased as the more general

"accumulation" to account for the state of the practice for ecological and health risk assessments.

Also, in the discussion on *page xiv (4th bullet),* the Panel indicates bioaccumulation is defined as a **persistent increase in steady-state levels**, which adds confusion to the wording proposed for the glossary, "net accumulation … that represents a **net mass balance between uptake and elimination**" *(page xiv, lines 31-34).* In summary, DOE suggests reviewing established terminology for ecological and health assessment practice and either using distinct definitions (in keeping with the approach the Panel recommends for "human biological monitoring," *page 59, lines 13-15*) or defining the general term as accumulation. If EPA does use the Panel's new definition of bioaccumulation in the Glossary, DOE would encourage the Agency to use the body of the Framework to discuss actual, practical applications for risk assessors in order to avoid confusion among risk assessors. That would allow the utility of the term to be retained for site-specific ecological applications and clarify differences for health applications. Using the main Framework to better frame concepts and thus avoid confusion regarding the Panel's terminology preferences that may not consider integrated risk assessment practice also extends to Panel comments that seem to confuse bioaccumulation and toxicity *(e.g., pages 7-8).*

3. <u>Speciation, cycling and transfer, and ambient levels</u>

a. Nature and type of source *(e.g., page xii, lines 26-27 and page 7, second section)*

In several places in their report the Panel comments that the nature and type of metals sources have not been identified in the Framework, and that the source plays an important role in the toxicity of essential metals. The objective of this statement is unclear because key to the bioaccessibility, pharmacokinetics (PK, including bioavailability), and pharmacodynamics (PD) of a metal is its physicochemical form (and levels) to which exposures could or would occur. That is, whether it was released from a photographic plant or and electro plating facility is relatively unimportant compared with the characteristics of the metal in the exposure setting. Also note that it seems unusual to reflect atmospheric deposition as a source (parallel to an electro plating facility, *page 7, line 16),* for that is commonly represented as an environmental transport process. DOE notes that the Agency's cumulative risk framework (2003) specifically orients risk assessors forward to place-based assessments from the older source-based approach. This means all metals in a given exposure/risk setting would be evaluated in an integrated manner, regardless of origin. Thus, it would be useful if the Panel clarified the intent of its comments on the importance of the nature or type of source.

b. Speciation and direct measurement *(page xi, first bullet, and pages 8-9)*

DOE encourages the Panel to reconsider its definition of speciation in light of practical implementation for metals risk assessments, which is the focus of the Framework. (The proposed definition could be confusing to many environmental and analytical chemists who commonly refer to this as fractionation.) Also, the intent of the Panel's comment regarding insufficient discussion of the direct measurement of speciation is unclear *(page 9, lines 21-22).* Historically the vast majority of metals

measurements have been made by atomic absorption or emission spectrometry, which converts all species to elemental atoms so information on speciation is lost. Speciation has thus been approached in two ways, with the much more common practice being through thermodynamic modeling as described in the Framework, using site-specific data on pH, eH, complexing species present, and other contributing factors. The second would be by measuring certain species using specialized or emerging analytical methods, which is more a future direction of the art. If the Panel aims to encourage that direction, it would be useful to not imply this is a routine approach, and to provide context regarding the limitations for direct measurement of metal species.

c. Biogeochemical cycles *(page 10, lines 17-28, repeated on p. 21)*

The point of the comment is not clear because overview discussions of this topic are provided at a useful level in the Framework (e.g., see Section 4.1.9), as biogeochemical cycles involve transformations between organic and inorganic forms with intermediate steps involving interconversions (note for *lines 24-25, page 10* that carbon would seem more commonly limiting than metals). It would be useful for the Panel to indicate the practical purpose served by extending discussions of this topic within a Framework the Agency has defined as focusing on inorganic metals.

d. Bulk sediment numbers *(page 73, first paragraph)*

DOE agrees with the usefulness of suggesting alternative guidance where AVS-SEM data are unavailable. But in suggesting other approaches such as bulk sediment data, it is important to state what metal information and criteria (SQC, TEL and PEL) must be available for them to be useful. The Panel should also clarify how bulk sediment concentrations would be applied at the national scale, considering differences in how data are collected (e.g., averaging over depth or total concentration irrespective of dissolved state or speciation used) and variations across regions that can limit the relevance of a lumped approach.

e. Background and ambient levels *(page 16, third bullet, page 58, and elsewhere)*

DOE agrees with the importance of clearly defining the terms ambient and background, but the Panel's recommendation is counterproductive. Both of these terms are in common use in ecological and human risk assessments because they allow important distinctions to be made. So to delete "background" and replace it with "ambient" *(page 58)* would increase confusion and the potential for misinterpretation. It would be more reasonable to retain both terms and simply clearly define the two, as is done in current practice (e.g., with background representing naturally occurring levels and ambient including anthropogenic contributions). This would retain consistency with terminology in other EPA documents, including the conceptually similar cumulative risk framework (2003). (Note this comment further supports the point regarding usefulness of distinct definitions as a practical matter, as discussed in Specific Comment 2a.) Thus, the Panel should consider the practical implementation emphasis of the Framework and delete the request to collapse these into one term. To illustrate the confusion associated with unclear terminology, consider the statement "The SAB notes that

arsenic, for example, is naturally occurring but still needs to be regulated" *(page 16, lines 36-37, repeated later).* This seems to imply that sites are expected to bring naturally occurring levels into compliance with a particular regulatory level. (Note that this is a risk management issue, and therefore need not be part of a risk assessment framework.) The Panel's recommendation that the Framework "provide guidance to establish a background concentration" is also confusing (and somewhat contradictory with earlier statements) and also appears to be outside the scope of a framing document (see General Comment 3). The Panel should explain what is intended by this comment and should retain both terms in accordance with common risk assessment practice.

4. Bioaccessibility vs. biovailability

The Panel (like the Framework document) seems to often use the terms bioavailable/ bioavailability when discussing bioaccessible/bioaccessibility *(e.g., pages xiii, line 13 and elsewhere).* From the definition provided in the Framework, DOE understands that bioaccessibility represents the environmentally available component, while bioavailability addresses absorption across the exchange boundary, upon uptake or intake. (Note that this definition of bioavailability is consistent with its use in medicine/pharmacology, consider oral bioavailability). The Panel should revisit its use of this term to be consistent with the Framework definition and scientific practice.

5. Body burden and biomonitoring

DOE disagrees with the Panel's statements that "Section 4 of the Framework does not adequately describe biomonitoring" *(p. 59, lines 17-18)* and "lack of discussion on this topic is a serious deficiency of both Sections 3 and 4 of the Framework" *(page 59, lines 30-31).* Noting that issues raised in the comment and limitations in the current science are acknowledged in Sections 4.2.2.1, 4.2.2.4.1, and 4.2.4.3 and elsewhere in the Framework, the DOE considers the discussion in that document to be at an appropriate level for a framework (see General Comment 3). Also, in the Panel's discussion of body burden (*(page 59),* measurements often do not represent steady state, and it is not clear how the indicated "baseline" is equivalent to background (rather that would seem to parallel "ambient" by analogy to the background issue for environmental levels). Thus, the changes suggested by the Panel could increase confusion in interpreting terms for metals risk assessments. The Panel should review its terminology to be more consistent with standard risk assessment practice and revise or delete the suggestion.

6. Toxicity and essentiality

a. Pharmacodynamics vs. pharmacokinetics

The Panel should re-evaluate statements throughout its report to avoid confusing distribution/accumulation with toxicity – or pharmacokinetics (which covers the basic processes of absorption, distribution, metabolism, and elimination, essentially reflecting the action of the body on the metal) with pharmacodynamics (which addresses the mode or mechanism of toxic action, to essentially reflect the action of the metal on the body). The distinction between these is very important, and the draft

SAB report should be revised to be consistent with standard terminology and scientific knowledge.

Also, the Panel's statement "Pharmacokinetic models can be used to estimate the extent to which metals bioaccumulate in tissues" *(page 8, lines 7-8)* could be misinterpreted as implying that models exist for all metals (far from it, as explained in the Framework Section 4.2.4.1). In addition, the Panel does not acknowledge the importance of exposure duration, time, and timing, stating only that the rate depends on the "concentration of the exposure dose and the frequency of exposure" *(page 8, lines 6-7).* This wording ("concentration of the exposure dose") is very confusing, given that concentration and dose are distinct terms with different units and meanings. Thus, the Panel should review its discussions of PK and PD to more accurately reflect accepted scientific terminology for risk assessment.

b. Reference values and potency factors

Several statements made by the Panel regarding these toxicity values are confusing. It is not true that human health risk assessors start their analysis with a metal-specific reference value and/or cancer potency factor *(pages xiv-xv and page 8)*. Note that many assessments do not involve these values at all, including those focusing on epidemiological analyses; even for those assessments that do consider these values, they are simply not available across exposure routes for many metals of interest (consider tungsten and tellurium, seemingly strange choices for the Panel to call out as metals that may be important, *page 20, last bullet*). Also consider the model used for lead, and note that even for Superfund applications the analyses start at a point much different from a toxicity value (consider data collection).

In addition, the wording "appropriately integrate" *(page xiv, line 41)* seems odd, as estimated doses are simply divided or multiplied by the indicated value to produce the index/indicator for noncancer effects or the cancer risk estimate. Furthermore, statements regarding the role of the "human risk assessor" *(page 8, lines 18-19)* seem to imply that the individual assessor may modify these values for various situations, when in fact they reflect standard values developed through a peer review consensus process and are not subject to change by general risk practitioners. Thus, the Panel should clarify what this overall comment is intending to suggest for the Framework.

c. Essentiality

The SAB panel "… recommends that the discussion of essentiality in the Framework be limited to humans …" *(page 61, 6.3.9.2, number 2).* This appears to contradict other parts of the report on essentiality (e.g., see *page 16, 2nd bullet, and page 68, #7*). DOE strongly disagrees that essentiality should be limited to humans, because essentiality is important in ecological assessments as well. This recommendation should be deleted.

Also relevant to Comment 6b above, the Panel's statement that "RfD/RfC values are presented as increments to RDAs" *(top of page 28)* is not true. The RfD/RfC is for a total daily exposure (dose/concentration), not an increment to an essential level. This should be corrected.

d. Low-dose effects *(page 41, fourth bullet)*

DOE disagrees with the Panel's comments regarding the omission of any discussion in Section 4 of toxic effects of metals at low doses, as the Framework includes considerable discussion relevant to this topic. The Panel states "… a number of metals exhibit a biphasic dose response curve with distinct adverse effects at low doses and a different type of toxic effect response at higher concentrations. The SAB recommends the inclusion of a section in the Framework that describes low dose toxic responses to metals and their compounds." This is included in Section 4.3 of the Framework (including Figure 4-4). More importantly, DOE suggests the Panel revisit its subsequent statement ("For example, it is now apparent that the slope describing Pb toxicity versus blood Pb concentrations is greater at lower exposure levels.") to better reflect scientific knowledge, notably in light of scientific evaluations by the Centers for Disease Control and others. (See http://www.cdc.gov/nceh/lead/ACCLPP/SupplementalOct04/Work%20Group%20Draft%20Final%20Report_Edited%20October%207,%202004%20-%20single%20spaced.pdf.)

e. Mixtures

Regarding the Panel's comment to discuss metal-organic interactions (e.g., arsenic and PAHs, *page 18, line 4)*, note that an illustrative discussion of metal-PAH mixtures is included in Section 4.3.6.3 of the Framework. Similarly, regarding the request for a discussion indicating that metals can react with organics to form organometallic compounds" *(page 18, lines 7-8)*, DOE notes that the Framework includes such discussions (e.g., see Section 4.1.9.2). The Panel should identify what is new in the request and what objective it will address. A similar comment applies to the Panel's request to cite the 1988 NAS reference *(e.g., pages 28-29)*. That is, it would be helpful to be clear on what new information and objective is being addressed, because the EPA mixtures guidance (which is discussed in the Framework) covers these issues in fair detail, including statistical analysis, information quality, and quantitative uncertainties.

The 1988 NAS book focuses on testing strategies, not risk assessment, and much more recent references are more relevant to the purpose of the Framework. The EPA guidance on mixture risk assessment, which is much more complete and focuses on information useful to risk assessment, is already included in the Framework. (Note that EPA's mixtures guidance from 2000 does cite the NAS 1988 text, including its limitations concerning interaction terminology, and goes beyond that early reference to address the magnitude of interaction, not simply the direction.) DOE agrees with the importance of good statistical analyses, and agrees that proper objective criteria and correct statistical tests are important. However, if statistical analyses are to be included then other characteristics should also be mentioned, such as toxicological evaluation of the relevance of experimental scenario to the asssesed setting, including the extent of extrapolation. Those characteristics, like statistical analysis, are part of a good risk assessment.

Many published toxicologic interactions are not likely to occur under environmental exposure conditions, often because of the lower doses. On this point, it would be useful if the Panel provided examples of dramatic effects observed, with an emphasis on environmental levels *(page 9, lines 36-37).* Also, most toxicologic interactions depend on the exposure route and duration (and sometimes sequence), and for metals, on nutritional status as well. Thus, a considerable amount of information is needed about the exposure scenario – at least the dose, duration, route, target organ, test species, timing, and other specific conditions as warranted – and about how specific the interaction is to that scenario, to be useful for a risk assessment. The Panel should clarify the objective of the additional information requested for mixtures.