Summary Minutes of the Science Advisory Board Metals Risk Assessment Framework Review Panel Public Teleconference
Tuesday, April 5, 2005, 12:00 – 3:00 p.m. EasternTime

Panel Members: See Panel Roster – Appendix A

Date and Time: Tuesday, April 5, 2005, 12:00 p.m. – 3:00 p.m. Eastern Time

Purpose: The purpose of the meeting was to discuss the draft report of the panel and identify any changes that might be needed to reach consensus on the report.

Attendees: Chair: Dr. Deborah Swackhamer

Panel Members:
Dr. David Dzomak
Dr. Kevin Farley
Dr. Ivan Fernandez
Dr. Bruce Fowler
Dr. Andrew J. Friedland
Dr. A. Jay Gandolfi
Dr. Joshua Hamilton
Dr. Kim Hayes
Dr. Robert Hudson
Dr. Thomas La Point
Dr. Samuel Luoma
Dr. Glenn Miller
Dr. James Shine
Dr. Katherine Squibb
Dr. William Stubblefield
Dr. Bernard Weiss
Dr. John Westall
Dr. Herbert Windom
Dr. Judith Zelikoff

EPA SAB Staff:
Dr. Thomas Armitage, Designated Federal Officer
Dr. Anthony Maciorowski, Associate Director
EPA Science Advisory Board Staff Office

Other EPA Staff:
Steve DeVito, EPA Office of Pollution Prevention and Toxics
Anne Fairbrother, EPA National Health and Environmental Effects Research Laboratory
Priscilla Halloran, EPA Office of Solid Waste
Rick Hertzberg, EPA Office of Research and Development
Erin Koch, EPA Office of General Counsel

Pamela Noyes, EPA National Center for Environmental Assessment
Randall Wentsel, EPA Office of Water
William Wood, EPA National Center for Environmental Assessment

Others Participating: Nancy Beck, U.S. Office of Management and Budget
James Laity, Office of Management and Budget
Debra Littleton, U.S. Department of Energy
Jane Luxton, King and Spalding, LLP
Margaret MacDonell, Argonne National Laboratory
Amy Perbeck, Michigan Department of Environmental Quality
Pat Phibbs, Bureau of National Affairs
Ann Smith Reiser, Asincorp.
Bruce Stiner, Steel Industry

Meeting Summary

The discussion followed the issues and timing as presented in the meeting agenda (Appendix B)

1. Convene Meeting, Call Attendance

Dr. Thomas Armitage, Designated Federal Officer (DFO) for the SAB Metals Risk Assessment Review Panel convened the teleconference and called attendance. He noted that the teleconference was being held as a public meeting under the requirements of the Federal Advisory Committee Act (FACA). The DFO is present at all such meetings to assure compliance with FACA requirements. Meeting minutes were taken by the DFO for the teleconference. Dr. Armitage noted that the minutes would be certified by the panel Chair and made available on the SAB website.

2. Purpose of the Call and Review of the Agenda

Dr. Deborah Swackhamer, Panel Chair thanked the panel members for calling in and reviewed the teleconference agenda. She stated that the purpose of the teleconference was to discuss the draft report and identify any revisions that may be needed to reach consensus on the report. Dr. Swackhamer stated that before discussing revisions that may be needed in specific sections of the report, the panel would hear EPA comments on the report. The panel would then discuss any changes needed in specific sections of the report and hear any public comments.

3. EPA Comments

EPA staff provided comments on the panel's draft report. EPA staff expressed appreciation for the panel's effort to develop the report and described clarifications that would be helpful. EPA staff stated that in the report, the Agency would like to receive a "crisp" set of recommendations that respond to the charge questions. EPA staff noted that the draft report of the panel provides many recommendations at many levels throughout the text, and that it is sometimes hard to understand what the recommendations are. The recommendations should be more clearly summarized in the report. EPA staff stated that they would like to see an executive summary that provides more detail and a clearer summary of recommendations in response to the charge questions.

EPA staff responded to SAB statements in the draft report indicating that the framework has a "dual personality," (i.e., parts of the document are a framework and other parts provide more specific guidance). EPA staff described the approach that was taken to develop the framework document. EPA staff noted that the framework document describes the state of the science in order to provide useful information for risk assessors. EPA staff stated, however, that in the framework the Agency does not want to get into the level of detail that would be provided in more specific guidance. EPA staff indicated that there would be opportunities accomplish this by developing more detailed "follow-on" documents to the framework. EPA staff stated that such documents can provide more specific guidance. However, given the initial text of the draft SAB report, EPA staff recognized that there may be an apparent imbalance in framework discussion of various aspects of science.

EPA staff noted that parts of the framework document address emerging science issues. Some of the recommendations in the draft panel report that focus on emerging science issues may require a considerable amount of time to address. EPA staff stated that the Agency would like the panel to look closely at the recommendations that have been provided and identify those that might be addressed in near and long terms. EPA staff also indicated that where possible it would be helpful to include examples to describe some of the recommendations provided.

4. Discussion of the Draft Metals Risk Assessment Framework Review Panel Report

Dr. Swackhamer thanked the EPA staff for their comments and asked panel members to comment on the draft panel report. She indicated that, based on initial comments from panel members, she would like to discuss the following topics: 1) the transmittal letter to accompany the report, 2) the executive summary, 3) the body of the report, 4) the length of the report, 5) additional references to be included, 6) the topic of whether the report should refer to "fugacity", and 7) the example table to be included in the report.

Dr. Swackhamer stated that the transmittal letter could be further developed after the next draft of the report is completed. One panel member stated that the draft transmittal letter that had been prepared captured the essence of the panel recommendations succinctly. Another panel member asked to discuss the points raised by EPA staff in their comments.

Dr. Swackhamer agreed to discuss these points. The first point discussed was whether the framework document had a "dual personality," (i.e., the purpose of the framework document - whether it is was developed as a framework or to provide specific guidance- is not clear). A panelist stated that follow-on documents could be developed to provide specific risk assessment guidance, but he noted that if the framework document was intended to provide both a risk assessment framework as well as useful guidance to risk assessors, it would be hard to avoid providing detailed information. Another panelist noted that EPA might want to consider developing a second document that would provide much more detail. Several other panelists noted that if the document was to serve as both a risk assessment framework and provide specific guidance, revisions would be needed and better balance in coverage was needed.

Another panelist noted that a major problem concerning the framework is the imbalance in coverage of various topics. Several panelists noted that inclusion of more examples in the framework would be helpful. The panel discussed how much detail was needed in the framework. A number of panelists commented that there could be more information in the framework to compare and contrast various assessment methods. A panelist noted that more detailed information could be provided in other guidance documents, but that the framework document should provide enough information to "set the philosophical framework." The panelist noted again that there is a problem in the framework in balance in coverage. A number of panelists commented that they believed there was a "dual personality" problem in the framework and that the SAB report should discuss this.

Dr. Swackhamer agreed that the framework document did appear to have a "dual personality" and that this should be addressed. She noted that the document should "err on the side of being a framework but provide some attention to detail."

Other panelists stated that additional detail was needed in the framework to achieve the appropriate balance in coverage and provide information about uncertainty in the science that is presented in the document. Panelists stated that the uncertainty associated with various models or approaches should be discussed in more detail. Panelists noted that the framework should contain a more detailed discussion of how various models or approaches should be used.

Another panelist agreed that the purpose of the framework was not clearly defined. The Metals Action Plan previously developed by EPA indicated that the Agency would develop both a risk assessment framework and specific risk assessment guidance. The panelist stated that EPA had apparently decided not to develop the guidance document, but that some risk assessment guidance had been included in the framework. This made the purpose of a framework document unclear. The panelist noted that improved clarity of expression was needed in the framework.

Dr. Swackhamer noted that it appeared to be the responsibility of various offices within EPA to produce their own program guidance documents. She noted that the panel could recommend that EPA offices develop individual guidance documents, and that the document reviewed by the panel be an overarching framework document. She noted,

however, that as discussed in the panel's report, there appeared to be agreement among panel members that the purpose of the framework was not clear, and that there was an imbalance in coverage that should be addressed.

Dr. Swackhamer then stated that she agreed with EPA staff comments concerning the need for clear identification and prioritization of the recommendations in the panel's report. She noted that it was important to more clearly identify and prioritize the recommendations to EPA. She stated that the executive summary in particular could be revised to more clearly and directly identify recommendations provided in response to the charge questions. Several panelists discussed editorial changes that could be included in the executive summary of the panel's report to more clearly identify the findings and recommendations. The panel discussed breaking some of the recommendations in the text into bullets. A panelist noted that one problem with the charge questions is that they cut across various sections of the framework document. Therefore it was not possible to address different sections of the framework separately. The panel discussed whether the charge questions should be listed in the executive summary of the panel report. Panelists expressed different opinions about this.

Dr. Swackhamer noted that the executive summary of the panel report should be written for EPA managers. She stated that in the executive summary it was particularly important to clearly summarize the recommendations provided in response to the charge questions. Several panelists commented that the executive summary in the current draft of the report was too long. Other panelists noted, however, that they did not want to remove too much of the information from the executive summary because they thought it captured the most important findings and recommendations in summary form. The panel then discussed removing specific lines of text on several pages from the executive summary.

Dr. Swackhamer then asked the panel to consider how to prioritize the recommendations in the panel report. She suggested that panel members should review the recommendations and determine whether they could be listed as short term (to be completed in less than six months) or long term.

The panel then discussed the issue of whether additional references should be included in the framework document. Several panelists noted that a more up-to-date discussion and references must be provided, particularly in the human health section of the framework document. A number of panelists agreed that it was very important that EPA provide these additional references.

Dr. Swackhamer asked whether any panelists had additional comments on the language in the panel report addressing bioaccumulation and accumulation. The panel discussed the specific language in the report and considered whether any revisions were needed. There was general agreement on the text in the panel's report.

Dr. Swackhamer then stated that one panel member had indicated that the term "fugacity" should not be used in the panel's report to describe metal behavior. Dr. Swackhamer

asked panelists whether a revision was necessary. Panel members agreed that "fugacity" should not be used in this context. More appropriate terms were suggested including, "chemical potential."

Dr. Swackhamer then asked the panel whether there were other specific issues to be discussed. One panel member noted that a statement on page 17, line 31 of the draft report was incorrect. Cr (III) was a nutritional supplement, not an essential metal. Panelists stated that this part of the report should provide a National Academy of Sciences reference, and the statement concerning the essentiality of Cr (III) should be removed.

Dr. Swackhamer then asked whether there were any panel comments on the example table that was included in the panel report. One panelist commented that the table in the report was very useful and appropriate to include as an example. Another panelist indicated that several changes were needed in the table if the biotic ligand model were included as an example. He agreed to provide these changes. Some panelists commented that a theoretical example should be included in the table. Others stated that the example in the table should not be confusing to readers. Panelists stated that a clear example should be chosen.

Dr.Swackhamer thanked the panelists for their comments and then asked whether panel members had additional specific comments on the draft responses to each of the charge questions. She asked the panelists to keep in mind EPA's comment that it would be helpful to prioritize the recommendations.

Several panelists offered additional comments on the response to charge question 1.1. The panel again discussed whether the framework document should provide both a risk assessment framework and specific guidance. Panelists noted that if the document is to serve both of these purposes it should do so consistently throughout. Panelists again mentioned the need to bring the framework up-to-date.

Panelists commented on the response to charge question 1.2 noting that the term "anthropogenic metals" should be changed to "metals released as a result of anthropogenic activities."

Panelists commented on the response to charge question 2.2, noting that some of the recommendations could be listed as "long term."

Panelists commented on the response to charge question 3.1. One panelist noted that he would recommend a number of editorial changes for the next draft. Another panelist commented that the recommendation concerning metals mixtures is a long term recommendation.

Dr. Swackhamer then asked if there were additional comments on any of the charge question responses. There were no additional comments. Dr. Swackhamer stated that she wanted to revise the report to clearly identify the recommendations and, where

possible, to prioritize them. To accomplish this, she asked the panel to provide written responses in three areas: 1) she asked each panel members to identify five statements or issues that should be included in the transmittal letter to the Administrator. 2) She asked each panel member to identify ten recommendations to be included in the executive summary. 3) She asked each panel member to look at all of the recommendations in the parts of the report that they had drafted and to identify the recommendations as short or long term. She asked that the panel members provide this information to the Designated Federal Officer by April 15. The report would then be redrafted to: 1) develop a new executive summary that more clearly identified recommendations in response to the charge questions, 2) include a new transmittal letter to the Administrator, 3) revise the responses to the charge questions to clearly identify the findings and summarize the recommendations, and 4) provide an indication of whether recommended actions were to be completed in the short or long term.

5. Additional EPA Comments

Dr. Swackhamer then asked EPA staff if they had additional comments. EPA staff stated that they appreciated the detailed recommendations provided on section 3 of the framework document. EPA staff noted that they will try to work on an example that could be included as a table in the framework, and also stated that the Agency would appreciate help on prioritizing the work that should be completed to revise the framework document. EPA staff also stated that they were working to develop a framework document that would be useful to a range of people.

Dr. Swackhamer thanked EPA staff for the additional comments and asked if there were public comments.

6. Public Comments

Debra Littleton of the U.S. Department of Energy provided public comments. The written text of her comments is provided in Appendix C.

Written comments were provided by William Adams, North American Metals Council. These comments are attached in Appendix C.

Margaret MacDonell, Argonne National Laboratory provided several comments concerning clarification of parts of the executive summary.

Jane Luxton, King and Spalding, briefly commented on the issue of using the term bioaccumulation with reference to human health, indicating that there must be recognition of the need to be careful in the use of this term.

7. Summary of Action Items

At the conclusion of the public comment period the Chair thanked panel members and EPA staff for participating in the teleconference and reviewed the next steps to be taken

in development of the SAB report. The Chair stated that another draft of the document would be developed to address comments discussed on the teleconference. The executive summary would be revised to provide a clearer summary of the recommendations in response to the charge questions. In the body of the report, recommendations would be clearly identified and, where possible, prioritized based on information to be provided by panel members. The Chair stated that she would send the next draft of the report to the Panel for approval. After panel approval, the report would then be sent to the Science Advisory Board for final approval and transmittal to the EPA Administrator. The Chair indicated that she believed review of the next draft could be completed by e-mail, and that another conference call would probably not be necessary. The Chair then adjourned the teleconference.

Respectfully Submitted:	Certified as True:
/Signed/	***/Signed/***
Thomas M. Armitage, Ph.D. Designated Federal Officer	Deborah L. Swackhamer, Ph.D. Panel Chair

APPENDICES

Appendix A: Roster of SAB Metals Risk Assessment Framework Review Panel

Appendix B: Teleconference Agenda

Appendix C : Public Comments

APPENDIX A - Panel Roster

U.S. Environmental Protection Agency
Science Advisory Board
Metals Risk Assessment Framework Review Panel

CHAIR

Dr. Deborah Swackhamer, Professor, School of Public Health, University of Minnesota, Minneapolis, MN

MEMBERS

Dr. Max Costa, Professor and Chairman, Department of Environmental Medicine, New York University School of Medicine, New York, NY

Dr. David Dzombak, Professor, Department of Civil and Environmental Engineering, Carnegie Mellon University, Pittsburgh, PA

Dr. Kevin Farley, Professor, Department of Civil and Environmental Engineering, Manhattan College, Riverdale, NY

Dr. Ivan Fernandez, Professor, Department of Plant, Soil, and Environmental Sciences, University of Maine, Orono, ME

Dr. Bruce Fowler, Assistant Director for Science, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA

Dr. Andrew J. Friedland, Professor and Chair, Environmental Studies Program, Dartmouth College, Hanover, NH

Dr. A. Jay Gandolfi, Assistant Dean for Research and Graduate Studies, College of Pharmacy, University of Arizona, Tucson, AZ

Dr. Joshua Hamilton, Professor, Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH

Dr. Kim Hayes, Professor and Director, Environmental and Water Resources Engineering Program, University of Michigan, Ann Arbor, MI

Dr. Robert Hudson, Associate Professor, Department of Natural Resources and Environmental Science, University of Illinois at Urbana-Champaign, Urbana, IL

Dr. Thomas La Point, Professor and Director, Department of Biological Sciences, University of North Texas, Denton, TX

Dr. Samuel Luoma, Senior Research Hydrologist, U.S. Geological Survey, Menlo Park, CA

Dr. Glenn Miller, Director, Center for Environmental Science and Engineering, University of Nevada, Reno, NV

Dr. James Shine, Assistant Professor of Aquatic Chemistry, Department of Environmental Health, School of Public Health, Harvard University, Boston, MA

Dr. Katherine Squibb, Associate Professor, Department of Epidemiology and Preventative Medicine, University of Maryland School of Medicine, Baltimore, MD

Dr. William Stubblefield, Senior Environmental Toxicologist, Parametrix, Inc., Albany, OR

Dr. Bernard Weiss, Professor of Environmental Medicine, University of Rochester Medical Center, Rochester, NY

Dr. John Westall, Professor, Department of Chemistry, Oregon State University, Corvalis, OR

Dr. Herbert Windom, Professor, Skidaway Institute of Oceanography, Savannah, GA

Dr. Judith Zelikoff, Associate Professor, Department of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

SCIENCE ADVISORY BOARD STAFF

Dr. Thomas Armitage, Designated Federal Officer, US EPA Science Advisory Board (1400F), 1200 Pennsylvania Avenue, NW, Washington, DC 20460

APPENDIX B – Meeting Agenda

SCIENCE ADVISORY BOARD
Metals Risk Assessment Framework Review Panel
Public Teleconference
April 5, 2005, 12:00p.m. – 3:00 p.m. (Eastern Time)

Draft Agenda

12:00 p.m.	Convene Meeting, Roll Call of Meeting Participants	Dr. Thomas Armitage Designated Federal Officer EPA SAB Staff Office
12:10 p.m.	Purpose of the Call and Review of the Agenda	Dr. Deborah Swackhamer, Chair
12:15 p.m.	Discussion of the Draft Metals Risk Assessment Framework Review Pane Report - Overarching comments and recommendations - Responses to charge questions 1 and 2 (Framework scope and assessment categories) - Responses to charge questions 3.1 – 3.4) (Framework recommendations; data, tools and methods; speciation; use of tables) - Responses to charge questions 3.5 - 3.7 (environmental chemistry comments) - Response to charge question 3.8 (natural background levels of metals) - Responses to charge questions 3.9 and 3.10 (human exposure and heath effects comments) - Responses to charge questions 3.11 – 3.14 (ecological exposure and effects comments)	Dr. Deborah Swackhamer and Panel
2:15 p.m.	EPA Comments	Dr. William Wood EPA National Center for Environmental Assessment
2:30 p.m.	Public Comments	Dr. Thomas Armitage Designated Federal Officer
2:45 p.m.	Discussion of Next Steps, Schedule and Process for SAB Approval of the Panel Report	Dr. Deborah Swackhamer, Chair
3:00 p.m.	Adjourn	

Appendix C – Written Public Comments

DOE Staff Comments on the Draft Report of the Science Advisory Board Metals Risk Assessment Framework Review Panel
Review of EPA's Draft Framework for Inorganic Metals Risk Assessment, Draft 3/29/05

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

The Department of Energy (DOE) has been extensively involved with the Environmental Protection Agency (EPA) Metals Risk Assessment Framework during the last several years and believes it is a strong and valuable document. The EPA Science Advisory Board (SAB) Review Panel for this Framework conducted a public meeting February 1-3, 2005, at which DOE provided limited input regarding initial Panel deliberations. In reviewing the draft SAB Review Panel report, DOE agrees with many comments but finds others that might introduce confusion to the Framework revision process. These public comments 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.

1. Document presentation and quality
   (e.g., p. xi, lines 26-27; p. xii, lines 4-10, repeated on p. 5, line 42, to p. 6, line 2)

   The DOE disagrees with the SAB Panel's statements that significant revision is needed to develop a document that is of high quality. The DOE believes the Framework is a high-quality 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.

   As a note, various SAB comments on the EPA Framework about reorganization and redundancy *(e.g., p. xi, lines 30-31)* would also seem to apply to the draft Panel report. This is as to be expected given that just like the Framework, the Panel report is a draft document that is being offered to solicit input before being finalized. (A fair bit of redundancy/ repetition seems to exist not just because of the way the draft report is organized but also within individual comments *[e.g., p. 8, lines 27-30 with lines 32-33, and within p. xv, lines 33-40, as repeated on p. 9, lines 9-16]*. Reorganization might help streamline this report and enhance its overall understandability.)

2. Content detail
   (e.g., pp. xvi, 9, 10)

It seems the Panel finds fault alternately with too much detail and not enough detail in the Framework, and the specific relevance to a practical assessment framework (versus extended scientific study) is not always clear. For example, the Panel asks that the document be revised to address such issues as genetic erosion (over the long term), and to address insufficient discussion of various detailed analytical tools or protocols *(e.g., to measure speciation, p. xvi, lines 15-16, repeated on p. 9, lines 37-38; or for data collection, p. xvi, lines 24-30, repeated on p. 10, lines 1-7).* Note that specific methodology details already exist to address a number of these procedures (including EPA guidance for data collection and evaluation), and the Framework does identify key information (e.g., see Section 4.1.8 if that document). Thus, it would not seem to be the purpose of the Framework to repeat those discussions in detail. Rather, the highly specific information being requested on focused topics or techniques would seem more relevant for those more descriptive, associated guidelines. Similarly, using the biogeochemistry comment as an example *(p. xvi, lines 32-43, repeated on p. 10, lines 9-19),* these cycles can involve transformations among organic and inorganic forms (i.e., with intermediate steps involving conversion from inorganic to organic forms and vice versa), and overview discussions are included in the Framework (e.g., see Section 4.1.9 of that document). So the point of the comment is not exactly clear with respect to practical usefulness for assessing metals, within a framework that has been defined as focusing on the inorganic forms. As a Framework, DOE believes the current document appropriately provides broad principles and methodological concepts, with additional discussions to help illustrate key concepts. Consequently, many of the SAB comments would not seem relevant to the Framework revision.

3. Trophic transfer
   (p. xiv, line 26; p. 14, line 38)

DOE disagrees that the Framework explicitly eliminated consideration of trophic transfer in toxicity determinations. The Framework's recommendations on food chain modeling include the use of available models that consider trophic transfer *(p. 3-31, lines 3-7).* In addition, EPA recommendations on "trophic transfer, biomagnification and dietary toxicity" (Section 3.2.5) state that trophic transfer of metals can be an important source of exposure (Framework p. 3-19, lines 9-10) and discuss methods to assess trophic transfer (p. 3-19, lines 17-32). Regarding the Panel's comment on defining trophic transfer *(p. 14, line 38),* DOE agrees that a definition should be included in the Framework.

4. Use of BCF/BAF
   (p. 34, lines 44-46, and elsewhere)

DOE agrees that the Framework language on BAFs/BCFs could confuse readers, as it states the limitations of these factors but then tells readers how to derive them. DOE agrees with the SAB's conclusion that "one cannot use a BAF or BCF ratio for national assessment or hazard ranking procedures…" *(p. 57, lines 23-28)* and encourages the Framework to make this clear. Further agreeing with similar

statements elsewhere in the Panel's report *(p. 55, lines 41-46; p. 56, lines 19-21)*, DOE believes the Framework needs to clearly state that BCF/BAFs should not be used in hazard ranking or national assessments, and they may be used in site-specific situations. (The discussion on how they should be derived in site-specific situations could be presented at that point.)

5. Terminology and glossary
(p. xiii, line 34, to p. xiv, line 15; repeated p. 7, line 23, to p. 8, line 5, and elsewhere)

As background, there is substantial EPA precedent for making terminology distinctions to guide risk assessments within and among general technical areas. For example, terms such as mode and mechanism of toxic action, point of departure, margin of exposure, toxicologic interaction, and complex mixture all have been defined by EPA to facilitate health risk assessments of individual chemicals and mixtures. To give an example of a terminology distinction between ecological and human health assessments, EPA has used the term critical body residues for ecological assessments, because metal measurements often reflect whole-body data. However, that term is not used for human health assessments; instead, tissue concentrations are used because whole-body data do not represent the basic approach (we don't grind up to extract or digest humans for an overall sample analysis). A number of other terminology distinctions exist for ecological and human health assessments, simply reflecting the data and practical analyses appropriate to each field. Thus, although many (not all) underlying principles are common, the scientific community of risk assessors applies a number of terminology distinctions to facilitate appropriate and effective assessments for each.

DOE notes that EPA has defined bioaccumulation in guidance for ecological assessments, and that term has long been applied to support practical assessments for trophic transfer, in combination with the terms bioconcentration and biomagnification. (The DOE agrees with the Panel's statement that bioaccumulation and bioconcentration factors do not apply for human assessments, as a simple reflection of a practical methodology distinction. Because humans are at the top trophic level, transfer to higher levels in the food chain is not relevant.) A similar basis exists for clarifying a distinction between the standard bioaccumulation term for ecological assessments, which is not defined as such in standard glossaries for human assessments; for those, **the parallel approach addresses accumulated concentrations in tissues, with an emphasis on the target tissue or site of toxic action.** Note that in ecological assessments, bioaccumulation is often taken to represent steady state (equilibrium conditions, e.g., reflecting laboratory studies), while for humans, metal distribution and intermediate redistribution within the biological retention time for that metal can be a very **dynamic process** with potential accumulation or sequestration in various compartments varying widely depending on multiple influences. Thus, for human assessments, a given measurement can reflect a snapshot in time for conditions specific to that individual at that time, including their recent exposure profile.

Nevertheless, as a general principle, DOE agrees that harmonizing terms can be a useful goal. However, for certain terms, that principle can make a joint definition so general (in having been reduced to cover both) that the benefit of its unique relevance for practical applications in the field for which it was defined is lost. Thus, if the general definition for this term of bioaccumulation as proposed by SAB is retained in the glossary, DOE would encourage the main Framework text to extend beyond that general descriptor to frame useful applications for risk practitioners, notably so it can still be practically applied as needed for ecological assessments.

This approach of using the main text of the Framework to clarify confusion that might otherwise arise from Panel definitions also extends to comments regarding bioaccumulation being related to toxicity *(e.g., p. 7, line 7).* Care must be taken to make correct statements, as other factors are of primary importance to toxicity, including pharmacodynamics and the individual's nutritional status (which can play a major role and was not mentioned here). Note that the discussion on this point neglects pharmacodynamics altogether (which addresses the mode or mechanism of toxic action, to essentially reflect the action of the metal on the body), and only discusses pharmacokinetics (which covers the basic processes of absorption, distribution, metabolism, and elimination, essentially reflecting the action of the body on the metal). Pharmacokinetics does not address toxicity, as seems to be implied by the end of the first sentence in this paragraph. Also unclear is the statement "Pharmacokinetic models can be used to estimate the extent to which metals bioaccumulate in tissues" *(p. 7, lines 44-45)*, because that might seem to imply that models exist for all metals and this is not the case, as explained in the Framework (Section 4.2.4.1). In addition, the discussion here 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" *(p. 7, lines 43-44).* Note that it is not clear what is meant here by "concentration of the exposure dose" given that concentration and dose are distinct terms with different units and meanings.

Furthermore, if this harmonization approach is to be proposed, it should be consistently applied. Thus, other proposed glossary additions should be revisited. For example, the separate biomonitoring definition proposed for use in human health assessment *(p. 48, lines 35-37)* should instead be harmonized to produce a single definition broadly applicable to both human and ecological assessments. Given the problems associated with general definitions, including losing the meaning and utility for the specific purposes for which they were developed (with elements unique to a discipline), the Panel's statement that recommended glossary revisions would make the definitions consistent with current science and reduce confusion to the readers *(p. 7, lines 16-21) is not well supported. To be most useful, DOE would encourage at least the main text of the Framework to describe terms as they are applied in practice for specific purposes within the distinct fields. Whatever the approach* (e.g., presenting a general, broad definition in the glossary with more specific framing in the text, or presenting a general definition followed by discipline-specific details), DOE encourages that it be applied consistently rather than selectively, and in general

believes that definitions that reflect the state of the science and practice would be more useful than a single general term.

Additional terminology input regarding the use of ambient versus background is offered in Comment 8, which also suggests the utility of complementary definitions rather than one consolidated definition.

As a minor note regarding confusing terminology, it is not clear why fugacity is identified as the relevant principle for bioaccumulation *(p. 13, line 25)* as this term is generally defined as referring to phase transfer for a pure material, which would not seem to apply to bioaccumulation of environmental metals.

6. Mixtures
(various pages, noted below)

DOE is confused by the implication that EPA has not acknowledged that mixtures are present throughout the environment, given that the Framework specifically makes this point in many places. Thus, the purpose of the comment *(p. xv, lines 31-40, repeated on p. 9, lines 7-16; p. 32, lines 21-22)* is not clear.

Also, the recommendation to cite the 1988 NAS book is confusing *(e.g., p. 24, line 24 to p. 25, line 6, and elsewhere). That book focuses on testing strategies, not risk assessment, and much more recent references would be more relevant to the purpose of the framework.* The revision recommended in this comment in particular is inappropriately detailed compared with other, current discussions of scientific knowledge. While the intent seems to be to describe good scientific practice, it seems limited and imprecise in its discussions of interactions and omits any recommendation for interactions to be relevant to the risk assessment being conducted. The EPA guidance on mixture risk assessment is much more complete and focuses on information useful to risk assessment, and those sources are already reflected in the Framework. (Note that the EPA 2000 guidance does cite the NAS 1988 text, including its limitations concerning interaction terminology.)

As a note, the recommended revision also seems incomplete in terms of additional details; if specific components are to be provided beyond the general categories, then more should be included (e.g., inhibition). Nevertheless, DOE agrees with the suggestion to identify the importance of good statistical analysis, and to emphasize the basic point that proper objective criteria and correct statistical tests are important *(also p. 36, lines 16-17).* However, if statistical analysis is to be included then other characteristics should also be mentioned, such as toxicological evaluation of relevance of experimental scenario to the setting being assessed, including the extent of extrapolation. Those characteristics, like statistical analysis, are part of a good risk assessment.

Regarding the statement about the insufficient discussion of interactions between metals and organic mixtures *(p. 36, lines 13-16),* this seems at odds with the scope of

the Framework. Regarding the comment "There is ample evidence of this from laboratory experiments with simple mixtures (e.g., arsenic and PAHs)" *(p. 16, lines 15-16; see also p. 36, lines 13-14)*, note that an illustrative discussion of metal-PAH mixtures is included in Section 4.3.6.3 of the Framework. Similarly, regarding the statement "it would be useful to include a discussion indicating that metals can react with organics to form organometallic compounds" *(p. 16, lines 17-19)*, note that the Framework includes such discussions (e.g., see Framework Section 4.1.9.2). The recommendation does not seem to include anything new, as the EPA mixtures guidance (identified in the Framework) covers the basic issues in fair detail, including statistical analysis, information quality, and quantitative uncertainties. Unless the scope of the Framework is to be expanded to include metal-organic mixtures, this particular recommendation may not seem directly useful.

The DOE generally agrees with the suggestions for expanding the mixture discussions *(p. 50)*. However, the suggestion *(p. 50, lines 15-16)* for a table listing typical interactions could lead to serious confusion or misinterpretation. As described, the table could give the impression that those interactions would always occur and be significant if the listed metals were present. If such a list were to be developed, it would need to include information on the exposure scenario – at least the dose, duration, route, target organ, test species, timing, and other specific conditions as warranted – as well as information regarding how specific the interaction is to that scenario. The last suggestion *(p. 50, lines 37-42)* seems unnecessary, but perhaps what was intended was to encourage following the 2000 EPA mixture guidance along with good statistical and toxicological practice in the experiment and data analysis. And as noted above, the NAS/NRC book *(p. 50, lines 44-46)* would not seem most useful because of its scope and date*, as many advances in experimental design and data analys*is *have occurred over the last 17 years.*

7. Reference values, cancer potency factors
(p. xiv, lines 31-44, repeated on p. 8, lines 8-22; p. 24, lines 1-8)

Several statements in this comment are confusing. It is not clear what is meant by the request to revise the document to explain that human health risk assessors start their analysis with a metal-specific reference value and/or cancer potency factor *(p. xiv, lines 33-35, and parallel on p. 8)*. Note that many risk assessments may not involve these values, including those focusing on epidemiological analyses; for those that do, e.g., for Superfund sites, the analysis starts at a point much before this. Also, the wording "appropriately integrate" 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. And statements regarding the role of the "human risk assessor" could be misinterpreted as seeming to imply that each risk assessor must assess the basis of the reference value to ensure that the value itself addresses the appropriate population (isn't this the human population?) and other factors. Further, the comment seems to suggest these values would be modified by the assessor for various situations, when they reflect standard values developed through a

peer review consensus process and not subject to modifications by practitioners routinely conducting risk assessments. Thus, it would be helpful to clarify what this overall comment is intending to suggest for the Framework.

In a related comment, the Panel statement that "RfD/RfC values are presented as increments to RDAs" *(p. 24, line 5)* is confusing. The RfD/RfC represents a total daily amount, not an increment to an essential level. It would be helpful to further clarify what is intended by that overall comment *(p. 24, lines 1-8).*

8. Ambient versus background
(e.g., p. 15, lines 2-3, repeated on p. 47, lines 37-38; p. 52, lines 18-20)

DOE disagrees with the Panel's statement that "The term background is often incorrectly assumed to connote 'natural' and therefore 'safe' or of no significant human or ecological concern." Nevertheless, DOE does agree that it is important to be clear when using these terms to limit possible misinterpretation. However, the proposed SAB approach and associated statements seem confusing. For example, some might interpret "The SAB notes that arsenic, for example, is naturally occurring but still needs to be regulated" *(p. 15, lines 2-3, repeated on p. 47, lines 37-38)* as implying that somehow arsenic is expected to bring its naturally occurring levels into compliance.

Regarding the recommendation to delete the term background and replace it with ambient *(p. 47, lines 28-34)*, given the very common use of the term "background" throughout ecological and human health risk assessments (including in numerous EPA guidance documents), it would seem more practical and useful to consider instead retaining both terms and distinguishing them generally as indicated (with background representing naturally occurring levels and ambient including anthropogenic contributions). This point further supports the use of individually useful definitions versus consolidated glossary terms (as noted within Comment 5), which also seems supported by a statement later in the draft Panel report *(p. 52, lines 18-19).*

In terms of the Panel's recommendation that the Framework "provide guidance to establish a background concentration" *(p. 52, lines 24-26)*, this seems a bit confusing (somewhat contradictory with earlier statements), and would seem to go beyond the scope of a Framework document (see Comment 2).

With regard to the Panel's proposed use of the term body burden *(page 48, lines 19-34)*, the measurements discussed often do not represent steady state, and DOE notes that baseline is not equivalent to background (rather it could parallel "ambient" versus pristine background conditions, following the analogy above). Thus, it would seem useful to revisit this discussion.

9. Biomonitoring
(e.g., p. 48, line 39, to p. 49, line 7)

The DOE disagrees with the Panel's statements that "Section 4 of the Framework does not adequately describe biomonitoring" *(p. 48, lines 39-40)* and "lack of discussion on this topic is a serious deficiency of both Sections 3 and 4 of the Framework" *(p. 49, lines 6-7).* 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 finds the discussion in that document to be at an appropriate level for a framework (see Comment 2).

10. Bioavailability
(e.g., p. 52, line 34)

Regarding the Panel's statement "Bioavailability is a useful concept and should be brought up into the Framework recommendations" *(p. 52, line 34)*, DOE agrees with its importance but notes that it has been included in Framework recommendations (see Sections 3.1.2.3 and 3.1.2.4). As a terminology comment, in various instances the Panel report (like the Framework document) seems to use the terms bioavailable/bioavailability when discussions are addressing bioaccessible/bioaccessibility *(e.g., p. 15, lines 17-20; p. 52, line 38).* From the Draft Metals Framework, DOE had understood that bioaccessibility was to be used to address the environmentally available component, while bioavailability was to address absorption across the exchange boundary, upon uptake or intake (consistent with how oral bioavailability is defined in the pharmacology context). It would be helpful if the intended use of this terminology could be clarified.

11. Atmospheric metals
(p. 14, lines 11-13)

It is not clear what is intended by the Panel's statement "With regard to atmospheric transport, it should be noted that most metals occur almost exclusively as particles in the atmosphere, and this affects how exposure occurs and the types of effects exerted on receptors" *(p.14 , lines 11-13).* The Framework already states that most airborne metals, with a few important exceptions (e.g., mercury and arsine), occur in particulate form, and that this requires certain considerations for the exposure assessment (see Framework Section 4.2.2.2.1); further text distinguishes between approaches for particles versus gases, and dermal sensitization/portal of entry effects are subsequently discussed. Thus, it would be helpful to clarify what new points were intended to be made here.

12. Low dose effects
(p. 35, line 44, to p. 36, line 4)

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 we find a considerable amount of information in that section relevant to this topic. Also, the following comment from the Panel is very confusing "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. For example, it is now apparent that the slope describing Pb toxicity versus blood Pb concentrations is greater at lower exposure levels" *(p. 35, line 45, to p. 36, line 4).* First, the effect first observed at the lowest dose (i.e., the critical effect) is accounted for in developing the standard reference values, so that addresses the low-dose response. If the point intended to be made is that other effects can be observed at higher doses, yes that could be further noted if needed in the Framework (including for mixtures, where such secondary or tertiary or higher effects observed at higher doses can be jointly considered with others affecting those common organs/systems). However, as written, the statement seems to imply these low-dose effects have been missed, which is not the case. Furthermore, the lead example offered in the last sentence does not seem to be related to this point, as it simply indicates that the slope of the curve changes beyond the low-dose region (similar observations are common for many chemicals, e.g., per saturation), but that does not mean the effects from low doses have not been addressed. Thus, it would be helpful to clarify what is intended by this overall comment.

13. Summary recommendation tables
    (p. 41, lines 25-34)

    DOE agrees with the Panel that summary tables would be useful and would also be difficult to prepare, but also believes the effort would be worth it because such tables would further strengthen the value of this excellent Framework as a significant resource for risk practitioners across a wide variety of metal assessments.

Comments Received from the North American Metals Council for SAB Metals Risk Assessment Framework Review Panel Conference Call on April 5, 2005

March 29, 2004

Via Overnight Delivery and E-Mail: armitage.thomas@epa.gov

Dr. Thomas Armitage
Designated Federal Officer
EPA Science Advisory Board (1400 F)
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Washington, DC 20460

Re: Comments on the EPA SAB's Deliberations on the *Framework for Inorganic Metals Risk Assessment (External Review Draft),* Docket ORD-2004-0017

Dear Dr. Armitage:

The North American Metals Council ("NAMC") appreciates the opportunity to provide comments as the Science Advisory Board continues its deliberations on the Framework for Inorganic Metals Risk Assessment (External Review Draft) (Nov. 2004, EPA/630/P-04068c) ("Framework"). NAMC is an unincorporated group of 31 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 Framework.

Our comments consist of the points made directly below in the text of this letter:

SAB Comments

The human health breakout group of the SAB strongly recommended that the Framework document "*not try to make the distinction between the use of the term 'bioaccumulation' to describe metal concentrations in aquatic and terrestrial organisms and the term 'accumulation' of metals for humans, this is not an accepted distinction in the scientific community. The panel believes that it is important to recognize that some metals (for example, Cd, Pb, and U) do bioaccumulate in the tissues of humans and that this bioaccumulation is related to the toxicity of these metals. The rate at which this accumulation occurs is dependent on the balance between the accumulation and elimination of the metal in the tissues of concern and thus is dependent upon the concentration of the exposure dose and the frequency of exposure. The extent to which metals bioaccumulate in tissues can be estimated by pharmacokinetic models. The panel recommends that the definition of the term 'bioaccumulation' in the glossary of this document should be modified to read: 'Bioaccumulation: The net accumulation of a metal in a tissue of interest or the whole organism that results from exposure from all environmental sources, including air, water, solid phases (i.e., soil, sediment), and diet, and representing a net balance of uptake versus elimination of the metal.*"

NAMC Response:

While the above statements set forth the opinions of the Panel on the definition of bioaccumulation (presumably for human health), this discussion misses several key points relative to bioaccumulation for human health assessment where the Panel could assist the Agency with clarity in its Framework document.

Differences between ecotoxicological and human assessment of bioaccumulation

The principal focus of aquatic and aquatic-dependent species bioaccumulation

assessments has been on whole organism bioaccumulation to assess the potential for trophic transfer. There has been limited use of specific target organs as diagnostic tools of exposure and exposure-linked effects. In contrast, human assessment of bioaccumulation has primarily focused on target organ assessment (kidney for cadmium, central nervous system for lead, liver for copper, etc). Differences in the way bioaccumulation data are assessed are important in terms of the decisions that are made with the data and whether or not a substance is judged to be "bioaccumulative."

Background information on bioaccumulation factors (BAFs):
BAF terminology was developed by aquatic toxicologists to describe chemical substance uptake by aquatic organisms for the purpose of assessing the potential for trophic transfer and potentially biomagnification. BAFs were initially developed primarily for fish and for non-polar organic substances. Laboratory experiments showed that octanol-water partition coefficients (log Kow) could be used as reasonable surrogates for BAFs since non-polar organic substances are lipid soluble and passively bioaccumulated. Consequently log Kow has been widely used as a surrogate to estimate "bioaccumulation." Both measured BAFs and log Kow have been used by EPA in its Waste Minimization Prioritization Tool (WMPT), by the Office of Water, and by the TRI office for designating bioaccumulative substances. EPA has used a cutoff BAF value of 1000 to separate bioaccumulative from non-bioaccumulative substances. While this approach is generally consistent with published literature, it is limited in its scope to aquatic organisms and is limited to use with organic substances. It cannot be applied accurately to inorganic substances due to the inverse relationship between exposure and accumulation.

While it is recognized that log Kow cannot be used to estimate bioaccumulation for metals for either aquatic or human life, there have been misuses of both BAFs and log Kow for human health "bioaccumulation" assessment including designation of bioaccumulative substances by the TRI and Office of Solid Waste (WMPT). Log Kow greater than 3.0 or BAFs greater than 1000 have been used to identify bioaccumulative substances for human health assessment. Both approaches are inconsistent with human health literature and the state of the science. Further, while criteria have been developed both internationally (United Nations, OECD) and within the US for selecting substances that are "bioaccumulative" for purposes of assessing bioaccumulation in a given organism or trophic transfer within aquatic ecosystems, there has been no parallel assessment scale developed for human assessment. This raises the question as to how a given substance is to be judged as being "bioaccumulative" or to bioaccumulate in humans. As far as we are aware, independent criteria appear to be lacking to determine when one substance is more accumulative than another or to define a given substance as "bioaccumulative."

The background paper on human health highlighted several important issues that did not receive the full consideration of the Panel. Metal accumulation in human tissues is different from the simple partitioning of non-polar organic compounds in that it is governed by physiological processes that modulate trace mineral metabolism and is often capacity limited. Cadmium accumulation is the result of metallothionein binding and the

substitution of cadmium at binding sites that would normally be occupied by zinc. Lead accumulation in bone is the result of active metabolic processes (bone remodeling) that incorporate lead into the mineral matrix of bone in place of calcium.

The panel seems to advise that physiologically regulated sequestration processes be equated with bioaccumulation, but no guidance is provided as to the metrics that should be applied in the interpretation of such specific interactions. Lead may accumulate in bone, but the concentration of lead relative to calcium in bone is roughly equivalent to the lead:calcium ratio in the diet – very little net enrichment relative to calcium occurs. Indeed, physiologically-based pharmacokinetic models for lead are essentially models for calcium metabolism adapted to the uptake and excretion properties of lead. If lead "bioaccumulates" in bone, should calcium also be labeled as such? If cadmium "bioaccumulates" in metallothionein-rich tissues, does the same label apply to any other substance (e.g. zinc or copper) that will similarly enrich?

In light of the foregoing, we suggest the following:

- It is recommended that the SAB Panel provide the Agency with criteria for assessing extent of human bioaccumulation if they are available. Absent these criteria, the Panel should make a clear statement indicating the limitations of the science for assessing bioaccumulation in humans and recommend the Agency develop guidance on human bioaccumulation assessment.
- The SAB should also clearly indicate that log Kow values or BAFs derived from aquatic studies are inappropriate for assessing human bioaccumulation.

Separating bioaccumulation from toxicity

"The panel believes that it is important to recognize that some metals (for example, Cd, Pb, and U) do bioaccumulate in the tissues of humans and that this bioaccumulation is related to the toxicity of these metals".

The Panel statement above, links bioaccumulation and toxicity in a way that implies that bioaccumulation would/could be interpreted in terms of toxic response. While toxic responses may result from accumulation at a target site, assessment of the extent of bioaccumulation to date for <u>regulatory</u> purposes has been carried out independent of toxicity. It is important for the Panel to be clear in its guidance on this point. The examples listed by the Panel actually illustrate the complexity of this issue. Cadmium accumulates in the human kidney and chronic exposure has been associated with manifestations of renal dysfunction. Levels of cadmium accumulation in the liver are normally higher than in the kidney, but the liver is not regarded as the principal target organ of concern. Similarly, lead tends to accumulate in bone, but this is not the principal target organ of concern. Rather, concerns for lead exposure focus upon central nervous system impacts. Bone lead is principally of interest as a surrogate measure of chronic exposure and, under highly specific circumstances, as an endogenous source of lead that can be mobilized for distribution to soft tissues that are the targets of toxicity. Both metals thus provide examples in which accumulation occurs at tissue sites that are

not the sites of principal concern to risk assessment.

- It is recommended that the Panel separate bioaccumulation as a hazard factor from toxicity as a hazard factor for purposes of providing the Agency clear guidance on human bioaccumulation assessment. This is important because the Agency uses bioaccumulation as an independent factor in hazard assessments.

Thank you for the opportunity to submit comments on the 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