UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

April 26, 2006

EPA-CASAC-06-005

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of the Agency's *Air Quality Criteria for Lead (First External Review Draft)*, *Volumes I and II* (EPA/600/R-05/144aA–bA, December 2005)

Dear Administrator Johnson:

EPA's Clean Air Scientific Advisory Committee (CASAC), supplemented by subject-matter-expert Panelists — collectively referred to as the CASAC Lead Review Panel (Lead Panel) — met in a public meeting held in Durham, NC, on February 28 and March 1, 2006, to conduct an initial peer review of the Agency's *Air Quality Criteria for Lead (First External Review Draft)*, *Volumes I and II* (EPA/600/R-05/144aA–bA, December 2005), also known simply as the 1st draft Lead Air Quality Criteria Document (AQCD). The current CASAC roster is found in Appendix A of this report, and the Lead Panel roster is attached as Appendix B. The charge questions provided to the Lead Panel by EPA staff are contained in Appendix C to this report, and Lead Panelists' individual review comments are provided in Appendix D.

The members of the Lead Panel were generally pleased with the quality of this 1st draft Lead AQCD, but regret the lack of an integrative synthesis chapter in this initial draft. The Lead Panel approved of the organization that was used in most chapters, *i.e.*, starting with a brief review of what was in the earlier previous AQCD, followed by the new information obtained since the publication of the earlier document, and ending with a short summary. However, the Lead Panel suggested that the beginning of the initial chapter should clearly state the question to be addressed, *i.e.*, Is there evidence that the current lead standards need to be made more (or less) stringent? In order to address this crucial question, the Lead AQCD needs to place greater emphasis on the adverse effects that occur at low levels of lead exposure. The Lead Panel was concerned that the document, as written, focuses too much on material relevant to occupational, high-level exposures. In addition, the Panel expressed concerns with respect to the superficial and incomplete discussion of neurobehavioral effects of lead exposure and the lack of update to the neurobehavioral literature published since EPA's issuance of the previous Lead AQCD.

1. Background

The CASAC, comprising seven members appointed by the EPA Administrator, was established under section 109(d)(2) of the Clean Air Act (CAA or "Act") (42 U.S.C. § 7409) as an independent scientific advisory committee, in part to provide advice, information and recommendations on the scientific and technical aspects of issues related to air quality criteria and national ambient air quality standards (NAAQS) under sections 108 and 109 of the Act. Section 109(d)(1) of the CAA requires that EPA carry out a periodic review and revision, where appropriate, of the air quality criteria and the NAAQS for "criteria" air pollutants such as lead. The CASAC, which is administratively located under EPA's Science Advisory Board (SAB) Staff Office, is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The CASAC Lead Review Panel consists of the seven members of the chartered (statutory) Clean Air Scientific Advisory Committee, supplemented by thirteen technical experts.

EPA is in the process of updating, and revising where appropriate, the AQCD for lead. Section 109(d)(1) of the Clean Air Act (CAA) requires that EPA carry out a periodic review and revision, as appropriate, of the air quality criteria and the national ambient air quality standards (NAAQS) for the six "criteria" air pollutants including lead. On December 1, 2005, EPA's National Center for Environmental Assessment National, Research Triangle Park (NCEA-RTP), within the Agency's Office of Research and Development (ORD), made available for public review and comment a revised draft document, *Air Quality Criteria for Lead (First External Review Draft), Volumes I and II* (EPA/600/R-05/144aA–bA). This first draft Lead AQCD represents a revision to the previous EPA document, *Air Quality Criteria for Lead*, EPA–600/8–83/028aF–dF (published in June 1986) and an associated supplement (EPA–600/8–89/049F) published in 1990. Under CAA sections 108 and 109, the purpose of the revised AQCD is to provide an assessment of the latest scientific information on the effects of ambient lead on the public health and welfare, for use in EPA's current review of the NAAQS for lead. Detailed summary information on the revised draft AQCD for lead is contained in a recent EPA *Federal Register* notice (70 FR 72300, December 2, 2005).

2. CASAC Lead Review Panel's Peer Review of the 1st Draft Lead AQCD

The initial peer review of EPA's first external review draft AQCD for lead took place in a public meeting held in Durham, NC, on February 28 and March 1, 2006. Specific comments aimed at improving the individual chapters of the 1st draft Lead AQCD are given below. These are aimed at pointing out omissions, places in the document where additional or more-balanced interpretations are needed, and sections where the organization of the AQCD could be improved. Responses to the charge questions are given either directly or indirectly in the comments on each chapter or, in some cases, in the individual comments of Lead Panel members attached to this letter (Appendix D).

In general, **Chapter 2, "Chemistry, Sources, and Transport of Lead**," is well-written and adequately summarizes pertinent information regarding chemistry, natural and anthropogenic sources and transport of lead in the environment. However, the information relative to production, active sources, emission rates, particle size, total lead emissions and ambient air lead levels is outdated or missing. For example, lead emission data from coal and

fuel oil combustion and some metallurgical processes rely, for the most part, on older references (*e.g.*, Pacyna, 1986). Accurate and informed emission inventory data are critical to provide a perspective in establishing and implementing protective health and environmental standards for atmospheric lead.

EPA has limited this review to "…where information is available in the peer-reviewed literature." However, data and better information for production, emissions, industry transition and economic indicators may be found in the trade literature and government agency records. The Lead Panel felt that, if adequate peer-review literature data do not exist, the use of publicly-available reports and reliable compilation of data is justified. In that event, data quality and reliability should be assessed and discussed as the material is incorporated in the document. If usable emission and source characterization data are unavailable or unsuitable for use in the standard setting process, the critical need to have these updated must be emphasized.

Other concerns with Chapter 2 are that it: (1) fails to put the various emission categories in context; (2) is somewhat fragmented; and (3) is not well-integrated with the remainder of the document. Putting the information into a broader historic, national and global context and acknowledging local problem areas in the U.S. would be beneficial. Several sources and source categories are listed, but it is not clear which are the most important ones. Some ranking should be provided. In addition, a number of additional examples that tie chemical and physical mechanisms in environmental and biological processes to material presented in later Chapters would be helpful. Since particle size information, for example, is scattered through different sections; a summary section or table would be useful.

Chapter 3 on **"Routes of Human Exposure to Lead"** is, in general, a good discussion of this field. There are, however, several modifications that would enhance the chapter, such as an overview and introduction. It would be helpful if there was a description of the scope of the systematic approach that was used to identify the critical papers on lead exposure published since 1990. There should be a stronger focus on the relative contributions of various sources of lead exposure.

Chapter 3 includes substantial information about dust lead as opposed to airborne lead. This is important because these two exposure sources are substantially interrelated. Moreover, dust is the most proximal exposure for contemporary children. The information on these two related exposure sources should be organized into two separate sections of Chapter 3 for clarity. The chapter should also include a discussion of how soil and road dust are affected by human activity. In addition, as was pointed-out during the meeting, this chapter omits information on studies that relate drinking water lead to blood lead, differences between first-flush, partially-flushed, and fully-flushed samples, *etc.* Since EPA is also in the process of revising its lead standard for drinking water, this information should be updated and included in this chapter.

The chapter should include insights that explain the contribution and trends in lead exposure. For example, it may not be obvious to all readers that the various sources of lead intake are cumulative, and that blood lead (in children) and bone lead (in adolescents and adults) are cumulative biomarkers of exposure. Residential exposures (*i.e.*, lead-based paint and lead-

contaminated house dust and water) have become increasingly important sources of lead ingestion following the phase-out of leaded gasoline and reductions in dietary intake.

This review should describe the relative contribution of various sources of lead exposure that vary by age using epidemiologic studies. For example, children's blood lead levels rise rapidly between six and 12 months of age, peak between 18 months to 36 months and then gradually decline. Lead-contaminated floor dust is a source of lead intake throughout early childhood, but lead-contaminated dust on windowsills is not a major source of intake until the second year of life, when children stand upright. Soil ingestion, as reported by parents, peaks during the second year of life and diminishes thereafter. It would be useful if the chapter summarized how our understanding of lead exposure has changed since the 1990 supplement. For example, there have been several randomized trials published since 1990 that provide insight into the relative contribution of lead intake from various sources that the chapter authors overlooked (*e.g.*, Haynes, 2001; Jordan, 2004; Brown, 2005; Aschengrau, 1994).

Finally, the chapter leaves the impression that exterior sources of lead are more important sources of lead in house dust than interior sources, such as lead-contaminated paint. This may be true for mining, milling or smelting communities, but it is not true for many older urban communities. There are also a number of relevant studies that document sources of lead in human dust that are not currently included in Chapter 3. (See Lead Panel members' individual review comments found in Appendix D.) A discussion of the efficacy of lead paint abatement should also be included in the chapter.

The authors have provided a good first draft of **Chapter 4, "Models of Human Exposure to Lead and Observed Environmental Concentrations**." They have captured most of the basic information needed to understand the strengths and weaknesses of the various kinetic-based dosimetry models for lead in humans incorporating the oral, dermal, and inhalation routes of exposure. The Lead Panel recognizes the need for models to relate blood lead levels to environmental lead concentrations. Some Panel members also recognize the potential utility of slope-factor (*i.e.*, epidemiologic) models for this purpose. There is some disagreement among Lead Panel members as to the most scientifically-valid approach for estimating blood lead levels from environmental lead media concentrations. Most Lead Panel members think the biokinetic and physiologically-based models are the most valid to use for estimating blood lead levels, while some feel that the slope-factor models are more appropriate. The various opinions of Lead Panel members on this issue are captured in members' individual review comments, which are attached as Appendix D. In any case, the CASAC wishes to emphasize that Agency staff needs to explore, carefully and in detail, the comparative usefulness of the slope-ratio models and the biokinetic- and physiologically-based models for the purpose of addressing:

- Short and long-term exposures;
- Low exposure concentrations;
- Relevant exposure routes and media types;
- Both site-specific and national average exposures; and
- All age ranges and sensitive populations.

An assessment of these issues should be reflected in the 2nd draft Lead AQCD.

In addition to the individual comments of Lead Panel members that are attached to this letter, the Lead Panel offers the following comments and recommendations to improve the chapter. The chapter is currently missing a "bottom line" as to which model or models would be the most appropriate for use in the assessment of potential risks in humans from exposure to lead. The Lead Panel does not consider the EPA "All-Ages" Lead Model (AALM) to be ready for "prime time" use in routine applications given that it is still in development. The material related to this model should be minimized or deleted altogether.

Numerous studies have been conducted that have related concentrations of lead in various media in and around people's homes with the resident's blood lead. Regression or slope-factor models that relate the blood lead to media lead have resulted from these efforts. There is also an international pooling project of such studies. These studies and slope-factor models should be summarized and reviewed, along with an assessment of their strengths and limitations comparable to the assessment that was done for the physiologically-based models.

The Leggett and O'Flaherty models are closer to being ready for use but still require more work before they can be regarded as the "workhorse" models for use in risk assessments for lead-impacted groups of individuals. That being said, there are instances where these models can be useful. For example, the O'Flaherty model is probably the most robust of the models in terms of estimating blood lead levels (chronic and transient) associated with "absorbed" doses of lead. To this degree, the use of slope factors that relate absorbed doses of lead to blood lead levels is perfectly valid and easily-conducted using the O'Flaherty model after stripping off its exposure modules.

The effective interface between modeling and epidemiological data as both relate to Pb NAAQS should include:

- the role of air Pb-related dust lead and dust lead loadings for children in light of new sub-10 μg/dl thresholds for adverse health effects;
- the hazards to children of dust lead per the EPA floor dust rule; and
- the multi-media impacts of existing lead levels in these media.

In addition, the Integrated Exposure Uptake Biokinetic (IEUBK) model should be validated by using it to predict the distribution of blood lead concentrations in the National Health and Nutrition Examination Survey (NHANES) data, using reasonable assumptions about exposure, and adjusted as necessary. Modeling of child Pb exposure via the IEUBK model should include lowering the not-to-exceed 10 μg/dl level that sets IEUBK distributions for percentile protections to a lower value consistent with current findings about Pb toxicity. Section 4.7 on Slope Factor Models needs to be expanded to provide results available from regression models derived from epidemiological studies. In addition, Section 4.8 (Model Comparisons) should discuss when the use of models derived from epidemiological studies might be preferable to use of mechanistic models for estimation of blood lead levels.

Chapter 4's appraisal of the IEUBK model's blood lead level predictions should acknowledge limitations identified in the literature (in particular, Bowers and Mattuck, 2001). The chapter should also caution against inappropriate superimposition of the lognormal distribution on the IEUBK model output to estimate the risk of having a blood lead level above a specified threshold. The IEUBK model should be modified in its exposure module to handle dust lead loadings from air Pb and loading-related intakes in children by ingestion. The chapter currently focuses on blood lead in children, but the epidemiology data provide results for adverse effects in adults as well. Thus, the Lead Panel recommends Chapter 4 provide more information for predicting blood lead levels in adults. The IEUBK model, which is the model most currently used, only addresses children up to seven years of age.

Finally, the chapter currently does not do an adequate job of addressing lead deposition and clearance by the inhalation route of exposure nor does it recognize the importance of the size of lead particles in determining where and how much is deposited in various regions of the respiratory tract. In addition, the authors need to address how these aspects vary for children compared to adults. More specifics are needed on the bioavailability of lead once it has been ingested, inhaled or absorbed through the skin. Information on model parameter values and variables should be included in an annex to this chapter.

Chapter 5, **"Toxicological Effects of Lead in Laboratory Animals, Humans and In Vitro Systems,"** could be better-organized to provide balanced treatment of the topics and reduce redundancies. There should be succinct conclusions at the end of each section. Specific suggestions for reorganizations are in the individual comments attached to this letter. The experimental animal behavior literature has shown comparable results that occur at blood lead levels corresponding to those at which such effects are seen in humans. Much of that literature has been reported since the last iteration of the lead air quality criteria document.

Unfortunately, however, the current draft Lead AQCD does not adequately or critically cover this literature, focusing instead primarily on neurochemical and electrophysiological effects of Pb. In addition, the blood Pb levels at which effects are observed is inconsistently reported. The experimental literature on Pb-associated behavioral toxicity has reported effects at levels of 10-11 μg/dl and has also resulted in significant new information related to further defining the basis of reported changes in IQ. For example, there are several studies examining changes in various aspects of attention, particularly sustained attention and impulsivity. These are not covered critically, and in fact, the interpretation that sustained attention is a major effect of Pb fails to consider contradictory findings, or the deficiencies in the one study that is cited, where the magnitude of the reported changes in sustained attention are minimal. Therefore, this section of the document requires significant revision. Also to be re-considered is whether the extensive coverage of the other aspects of nervous system effects requires reporting in such depth and detail. Moreover, the discussion of cardiovascular effects of lead jumps immediately into a discussion of studies suggesting potential pathways for the lead-blood pressure association, and should briefly summarize the earlier literature that established that association.

Finally, the Lead Panel had extensive concerns about Section 5.3 with respect to the superficial and incomplete discussion of neurobehavioral effects of lead exposure. Contradictory findings are presented and are neither explained nor evaluated in any depth. In addition, this

section does not update the neurobehavioral literature published since EPA issued its previous Lead AQCD. For example, potential lead-induced deficits in attention are not critically reviewed. These studies are particularly important as they relate to the behavioral mechanisms underlying cognitive deficits and no doubt relate to the changes observed in IQ. These concerns are reported in-depth in the individual comments of Dr. Cory-Slechta, which are found in Appendix D, beginning on Page D-6.

Although **Chapter 6**, **"Epidemiologic Studies of Human Health Effects Associated with Lead Exposures**," is well-organized in first presenting the findings from the 1986 and 1990 update of the previous Lead AQCD and then updating the published literature to 2005, it suffers from several aspects of the time pressure expressed by Agency staff at the meeting with respect to meeting court-ordered deadlines. The chapter was clearly put together by a number of writers and needs to undergo significant editing. In many places much of the material is repeated and many of the same studies are used in each of the sections. This leads to redundancy of presentation of material that all needs to be there but should be said only once.

More important for those using the AQCD who only read this chapter, there needs to be some place where the multimedia exposure sources are presented. Clearly there are multiple biomarker methods that are discussed to define exposure. This presents a significant advantage over other criteria pollutants; however, in many places the text reads more like a medical textbook and, particularly for the naïve reader, the fact that the toxin being discussed is for a multimedia environmental and occupational pollutant gets lost. Some brief summary of information contained in Chapter 2 needs to be included in this chapter.

There are several places where reference is made to the Annex Tables, particularly in the biomarker discussion and in the neurobehavioral sections. In large part the Lead Panel agreed with this approach. However, there are a number of places where a summary graph, analysis, or table in the text would be useful. This is particularly true in the neurobehavioral sections where important effects at low level of exposure are discussed. The later sections on Renal and Cardiovascular effects seem to have included sufficient tabular and graphic examples.

Furthermore, there are a number of specific issues that are discussed in detail in the individual comments attached. Several broad specifics are mentioned as follows:

- The issue of measurement error in outcomes and the implication of such errors need further discussion.
- The conclusion that a single blood lead is a relatively-poor index of body lead burden is too broad.
- The discussion that long-term lead body burden represents the "gold standard" for exposure is not the case. Acute exposures that affect blood lead levels may or may not change body burden but may be important predictors of adverse effects.
- The statement that there is no consistent evidence of effects in adults if competing risks are taken into account is unsupportable.

- While the section on neurobehavioral effects mentions the consistency with animal toxicology, this is not done with the blood pressure/cardiovascular effects where similar mechanistic data exist.
- The section on exposure misclassification needs to focus on the epidemiological implications.

With regard to the Agency charge questions related to this chapter, for the most part the reviewers believed that most of the questions could be answered in the affirmative. The exception was with Charge Question QF2a, which had to do with model selection. The pooled analyses used a log-linear analysis to quantify the lead-associated IQ decrements. It was not explicit in the write up of this work that the non-linear values observed were not due to the influence of the model. Several suggestions in the individual comments were made to help clarify this section.

Finally, several suggested data sets were offered to all Agency staff to test a number of the models considered. (These were provided to EPA in subsequent e-mails). These need to be incorporated in the next draft of the Lead AQCD.

Chapter 7, the critical **"Integrative Synthesis"** chapter, was not completed in time for the Lead Panel's review of the 1st draft Lead AQCD. NCEA-RTP is developing this chapter for the 2nd draft of the Lead document, which the Lead Panel is scheduled to review in June 2006.

Chapter 8, **"Environmental Effects of Lead"** summarizes a large fraction of the accumulated body of knowledge concerning the effects of "atmospherically-deposited lead" on the soils, sediments, waters, and biota of terrestrial and aquatic ecosystems. The chapter is well-organized, with clearly written summaries of terrestrial effects (8.1.1) and aquatic effects (8.2.1), along with more detailed information intended to be included as annexes.

Nevertheless, some significant additional intellectual work is needed in preparing the Second External Review Draft and especially its Executive Summary and the Integrative Synthesis chapter. Both of these additional sections should summarize scientific knowledge regarding effects of lead on both public health and the environment. The information in Chapter 8 needs to be presented in a way that is more directly relevant to the issue of whether the EPA Administrator should retain, increase, or decrease the present primary and secondary NAAQS for lead. Since secondary standards are often (neglectfully) set equal to primary standards, a key question is whether there are environmental effects that occur at lead concentrations lower than, or for indicators, forms, or averaging times different from, those that affect human health.

Very substantial decreases in air concentrations and atmospheric deposition of lead into the environment were achieved in recent decades. Thus, most current exposures of living organisms in natural and managed ecosystems are caused primarily by redistribution of environmentally persistent airborne lead compounds deposited in soils, sediments, and surface waters prior to the phase-out of leaded gasoline in the 1970s and 1980s. Chapter 8 specifically needs to more clearly indicate how any continuing environmental effects of lead might respond to changes in current and future atmospheric lead emissions, concentrations or deposition. The chapter might better help EPA prepare for such changes if it included a more complete and/or

balanced analysis of the status of new advances in the science relevant to environmental management of lead. For example, consideration of monitoring needs and the implications of dietary exposure and trophic transfer are needed, as is more balance in considering equilibrium partitioning in sediments and uses of the biotic ligand model. It would also be useful to consider how environmental effects of historically deposited lead or future increases in deposition (if current laws are relaxed) might be modified by land-use changes, or soil amendment treatments, or interactions with other pollutants, including other metals or acidifying pollutants, or with changes in climate and climate processes.

Members of CASAC were especially pleased to see the relatively-thorough discussion at the end of Chapter 8 regarding the alternative concepts of critical loads, critical limits, target loads, and target times that have been developed in European and Canadian scientific literature to guide the processes of decision making regarding both environmental and public health effects of airborne chemicals.

In conclusion, the Clean Air Scientific Advisory Committee and the Lead Panel encourage EPA in its continued efforts to protect the public health and our environment from adverse effects of ambient lead. The Committee looks forward to reviewing the 2nd draft Lead AQCD — and particularly Chapter 7, the Integrative Synthesis — and the first draft of the Agency's Lead Staff Paper. As always, we wish the Agency staff well in this important endeavor.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

Appendix A – Roster of the Clean Air Scientific Advisory Committee

Appendix B – Roster of the CASAC Lead Review Panel

Appendix C – Agency Charge to the CASAC Lead Review Panel

Appendix D – Review Comments from Individual CASAC Lead Review Panel Members

Appendix A – Roster of the Clean Air Scientific Advisory Committee

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)

CHAIR

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

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Dr. James D. Crapo, Professor, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. Frederick J. Miller, Consultant, Cary, NC

Mr. Richard L. Poirot, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Frank Speizer, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. Barbara Zielinska, Research Professor, Division of Atmospheric Science, Desert Research Institute, Reno, NV

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Appendix B – Roster of the CASAC Lead Review Panel

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
CASAC Lead Review Panel

CHAIR

Dr. Rogene Henderson*, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

Dr. Joshua Cohen, Faculty, Center for the Evaluation of Value and Risk, Institute for Clinical Research and Health Policy Studies, Tufts New England Medical Center, Boston, MA

Dr. Deborah Cory-Slechta, Director, University of Medicine and Dentistry of New Jersey and Rutgers State University, Piscataway, NJ

Dr. Ellis Cowling*, University Distinguished Professor-at-Large, North Carolina State University, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, Raleigh, NC

Dr. James D. Crapo [M.D.]*, Professor, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. Bruce Fowler, Assistant Director for Science, Division of Toxicology and Environmental Medicine, Office of the Director, Agency for Toxic Substances and Disease Registry, U.S. Centers for Disease Control and Prevention (ATSDR/CDC), Chamblee, GA

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

Dr. Robert Goyer [M.D.], Emeritus Professor of Pathology, Faculty of Medicine, University of Western Ontario (Canada), Chapel Hill, NC

Mr. Sean Hays, President, Summit Toxicology, Allenspark, CO

Dr. Bruce Lanphear [M.D.], Sloan Professor of Children's Environmental Health, and the Director of the Cincinnati Children's Environmental Health Center at Cincinnati Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, OH

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

Dr. Frederick J. Miller*, Consultant, Cary, NC

Dr. Paul Mushak, Principal, PB Associates, and Visiting Professor, Albert Einstein College of Medicine (New York, NY), Durham, NC

Dr. Michael Newman, Professor of Marine Science, School of Marine Sciences, Virginia Institute of Marine Science, College of William & Mary, Gloucester Point, VA

Mr. Richard L. Poirot*, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

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Dr. Joel Schwartz, Professor, Environmental Health, Harvard University School of Public Health, Boston, MA

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* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

Appendix C – Agency Charge to the CASAC Lead Review Panel

OVERVIEW OF SALIENT ASPECTS OF THE DECEMBER 2005 1st DRAFT LEAD AQCD AND ASSOCIATED CHARGE QUESTIONS FOR THE FEBRUARY 28 – MARCH 1, 2006 CASAC LEAD REVIEW PANEL PUBLIC MEETING

A. Format and Structure of the Draft Lead AQCD.

In developing the December 2005 1st Draft Lead AQCD, NCEA followed past CASAC advice to streamline the format of the document, in order to facilitate timely CASAC and public review by focusing more clearly on those issues most relevant to the policy assessment to be provided in the Lead Staff Paper. As described in Chapter 1 of the 1st draft Lead AQCD, chief emphasis is placed on interpretative evaluation and integration of evidence in the main body of the document, with more detailed descriptions of individual studies being presented in a series of accompanying annexes. Key information from lead-related literature previously assessed in prior lead NAAQS reviews is only succinctly summarized (usually without citation) at the opening of each section or subsection, to provide a very brief overview of previous work. For more detailed discussion of such information, readers are referred to EPA's 1986 Lead AQCD, an associated 1986 Addendum, and its follow-on 1990 Supplement. This format is intended to make each chapter of the main Lead AQCD a manageable length, to focus on interpretation and synthesis of relevant new research, and to lessen or avoid redundancy with previous Lead AQCD materials.

As for overall structure and content, after an introductory chapter (Chapter 1), the 1st Draft Lead AQCD presents chapters addressing three main topic areas:

- Characterization of properties of lead and its environmental dispersal, including discussion of: (a) the chemistry, sources, and transport (Chapter 2); and (b) observed environmental concentrations and routes of human exposure (Chapter 3);
- Pb-related health effects, including discussion of modeling of human exposure impacts on lead body burdens (Chapter 4), toxicological effects in animals, humans, and *in vitro* test systems (Chapter 5), and epidemiology studies (Chapter 6). (Please note that the integrative synthesis of Pb-related health effects will be included as Chapter 7 in the Second External Review Draft of the Lead AQCD, to be made available later in 2006 for public comment and CASAC review); and
- Pb-related welfare effects, including discussion of environmental effects of Pb on vegetation and ecosystems (Chapter 8).

Charge Questions A1. To what extent is the document format (*i.e.*, main chapters of the 1st draft AQCD focused on evaluative/interpretive aspects, with descriptive materials and tables presented in annexes) useful and desirable? Can the structure be further improved? If so, how?

B. Lead Chemistry, Sources and Transport (Chapter 2).

Chapter 2 summarizes available information on the chemistry, natural and anthropogenic sources, and transport of Pb in the environment. The discussion of lead's chemistry is limited to properties of importance in the environment and in biological systems. Industrial uses of lead are summarized in tables. Sources and transport mechanisms are described in greater detail. Important mechanisms for transport of Pb in the environment that are discussed include: advection, deposition, resuspension, runoff, leaching, aquatic cycling, plant uptake, and ingestion by livestock and wildlife. Advection in the atmosphere is the mechanism of greatest importance in this discussion. The major reservoirs identified are soils and sediments.

Charge Questions B1. Overall, does Chapter 2 provide adequate coverage of important chemical properties of lead and concise summarization of pertinent information on sources of Pb and Pb emissions, especially in relation to the United States? In particular, how well does Chapter 2 identify the most pertinent available datasets that contain information on emission rates for point and area sources? Also, does the discussion of available data adequately address issues such as the spatial distribution of point and area sources and emissions estimate uncertainties?

Furthermore, does the discussion satisfactorily address emissions by key industrial sectors? Does Chapter 2 adequately address other important issues relating to the dispersal and/or accumulation of Pb in the environment, *e.g.*, resuspension of roadside dust or the potential for Pb to accumulate in some media, like soils, due to its relatively low mobility? (The latter fact means that fairly low air Pb concentrations have the potential to produce elevated soil concentrations over time due to wet and dry deposition.) In addition, does the chapter adequately discuss key chemical and transport-related factors that should be considered in evaluating long-term buildup of Pb in the environment? Finally, are the discussions of the leaching of Pb from soil and sediment into surface and groundwater sufficiently complete for this chapter?

C. Environmental Exposure Pathways and Concentrations (Chapter 3).

Chapter 3 summarizes scientific information on routes by which humans are exposed to lead and the concentrations observed in pertinent environmental media, including air (*i.e.*, indoors, outdoors and occupational settings) and soil and dust (near-point sources, roads, and in urban settings). The available information on lead found in drinking water, food, and other sources (*e.g.*, paint, dietary supplements, pottery glazes, window blinds and hair dye) is also discussed. The techniques used for measuring environmental Pb concentrations are described so as to provide background for the reader on detection issues and potential sources of uncertainty. Available evidence indicates that Pb concentrations are elevated in all environmental media in urban areas. Highest concentrations are found near stationary sources and roadways. The most

important routes of exposure in the U.S. are by ingestion of food and waterborne lead or, in some areas, via contact with soils and/or house dust contaminated with Pb from deteriorated older leaded paint or from secondary deposition of airborne Pb from smelter emissions.

Charge Questions C1. Does Chapter 3 provide adequate coverage of pertinent available information (especially as it pertains to the United States) on Pb exposure routes, as well as environmental Pb concentrations, including those in air, drinking water, food, soils, and dust? Also, does the chapter delineate adequately interconnections between airborne Pb and its potential contributions (via secondary deposition) to Pb in other media (*e.g.*, indoor dust)?

Moreover, given the potential importance of historical deposition of Pb from mobile sources, does the chapter adequately identify key sources of information characterizing the magnitude and distribution of lead soil concentrations near roadways in urban, suburban and rural areas? Also, given the importance of characterizing "background" Pb concentrations in conducting health/ecological impact analyses (where background refers to both natural and generalized anthropogenic contributions as distinct form specific point sources), does the chapter adequately denote key sources of information characterizing existing "background" Pb levels in urban, suburban and rural/pristine areas?

D. Modeling of Lead Exposure Impacts on Internal Lead Burdens (Chapter 4).

The multimedia nature of Pb exposure must be considered in making decision on standards to lessen risks for adverse health effects projected to be associated with Pb exposures of susceptible populations. Scientific rationales underlying most EPA lead-related regulatory or remedial action decisions typically include estimation of the impact of exposures to Pb in air, water, food, soil/dust or other media on internal Pb body burden indices, for example, blood or bone Pb levels. Chapter 4 discusses historical evolution of the modeling of external Pb exposure impacts on internal Pb body burdens in various tissues, especially those widely used to index increased risk of Pb-induced health effects (*e.g.*, concentrations in blood and bone). This includes modeling activities related to development of EPA's 1978 Lead NAAQS and the generation of the EPA Integrated Exposure, Uptake, Biokinetic Model for Lead (*i.e.*, Lead IEUBK Model) in the late 1980s. The IEUBK Model has provided a tool for estimating distributions of blood Pb levels among pediatric populations less than six (< 6) years old likely to result from exposures to varying levels of lead from one or another media. As such, it has been widely-used to support development of standards or guidance for control of Pb in air or drinking water or remediation of Pb-based paint and Pb-contaminated soils and house dust. During recent years, EPA has also initiated efforts to further refine and expand the Lead IEUBK Model and its software to create an All-Ages Lead Model (AALM), which not only estimates the impact of Pb exposures from various media on blood lead levels in young infants and children < 6 yrs. old (as per its progenitor, the IEUBK Model), but also aims to project Pb exposure impacts on blood and bone Pb of older children and adults through age 90 years (as well as the unborn fetus exposed via transplacental transfer of Pb). Thus, the AALM aims to broaden the array of potentially-susceptible population groups that can be more readily evaluated with regard to the extent to which various Pb exposure scenarios may pose risks of undue elevations of internal Pb body burdens and associated health impacts.

Charge Questions D1. How well does Chapter 4 concisely characterize key information on: (a) the evolution and key features of important available approaches to the modeling of external Pb exposures and their impacts on internal Pb body burdens; and (b) the status of model evaluation efforts, *e.g.*, PBPK model code verification and comparisons of model-predicted versus observed impacts on blood or bone Pb distributions of particular lead exposure scenarios for affected population groups? Also, does Chapter 4 sufficiently characterize the ability of different models to handle key factors related to lead exposure modeling, including: temporal variation in external exposure profiles; low-level lead exposure; multi-pathway lead exposure; and the contribution of historical/artifact lead exposure in influencing blood lead levels?

Furthermore, given that the October 2005 SAB review of the AALM suggested that further model validation and verification was needed before the AALM should be used in support of regulatory development, does Chapter 4 clearly identify which alternative models (*e.g.*, IEUBK, O'Flaherty) should be used for adult and/or child modeling instead of the fledgling AALM? In addition, does Chapter 4 adequately identify the strengths and weaknesses of the recommended models in modeling adult and child populations? Finally, overall, how can Chapter 4 be improved without notable extension of length?

E. Toxicologic Evaluation of Lead Health Effects (Chapter 5).

An extensive lead toxicology literature is available, derived from controlled laboratory experiments carried out in various laboratory animals, including primates. Chapter 5 mainly focuses on newer scientific literature that has accumulated in the past 15 years or so since the last prior Pb criteria review. This includes discussion of interesting new findings elucidating novel information regarding lead effects on cardiovascular system and immune system functioning, as well as impacts on bone and teeth, in addition to new insights into effects on more traditionally-recognized lead target organs and tissues, *e.g.*, the nervous system, the renal and hepatic systems, and blood components.

Charge Questions E1. Have any important new animal toxicology studies been overlooked in Chapter 5 discussions on short- and long-term effects of Pb? Also, what guidance can be provided by the CASAC Lead Review Panel with regard to the following sub-questions or -issues?

E1a. Discussions in the neurotoxicology section focus mainly on lead effects on glutamatergic synapses, synaptic plasticity, protein kinase C, and sensory systems and learning. Are there any other areas pertinent to Pb neurotoxicology now missing or inadequately covered in this section?

E1b. To what extent does the existing scientific literature provide evidence for developmental Pb toxicity having a permanent impact on bone and teeth structure and for these tissues serving as Pb storage pools forming long-term internal sources of lead exposure for other body tissues?

E1c. Are the animal toxicology studies with chelation/intervention agents relevant to analogous studies in humans, and is the discussion of such studies of sufficient relevance for current purposes to include coverage of them here?

E1d. Do the newer insights gained on Pb-induced micro molecular alterations on erythrocyte biology, Pb-binding and transport kinetics, and altered nucleotide pools suggest molecular mechanisms of action? Are they suggestive of mechanisms underlying specific health endpoints?

E1e. Does the oxidative stress theory appear plausible for Pb toxicity and perhaps represent a common mode of action operating across organs and species?

E1f. Concentrations of Pb compounds used in animal toxicology studies often appear high and not necessarily very representative of ambient exposure scenarios. What advice can the Panel provide to identify a cut-off value for utilizing the biochemical and molecular toxicologic observations obtained under these exposure conditions in extrapolating animal toxicology study findings to humans in later development of an integrative synthesis chapter?

F. Epidemiologic Studies of Lead Exposures and Health Effects (Chapter 6).

Chapter 6 mainly assesses evidence derived from epidemiologic studies on associations between both short-term and long-term biomarkers of Pb exposure and various health endpoints. Such endpoints include: neurotoxic effects of lead in children and adults; renal effects; cardiovascular effects; reproductive and developmental effects; genotoxic and carcinogenic effects; effects on the immune system; and effects on various other organ systems. Important new findings from numerous studies have been published since the 1986 Lead AQCD/Addendum and the 1990 Supplement — including, perhaps most notably, evidence for increased risk of neurotoxicity in children at low blood Pb levels below 10 μg/dL. Numerous issues are discussed in Chapter 6 with regard to assessing: (a) the credibility of newly-reported findings being attributable to Pb acting alone or in combination with other potential confounders (*e.g.*, socioeconomic status and home environment, inter-individual variability in susceptibility to Pb toxicity); and (b) the health significance of changes observed on an individual or population basis. EPA is seeking advice from the CASAC Lead Panel with regard to the following questions or sub-issues related to Chapter 6.

Charges Questions F1. Different biological markers of Pb exposure and body burden are discussed in Chapter 6. The discussion concludes that higher blood Pb concentrations can be interpreted as indicating higher exposures (or lead uptakes), but do not necessarily predict appreciably higher body burdens. Bone lead is considered an indicator of cumulative Pb exposure, with Pb in the skeleton being regarded as a potential continuing internal source of Pb exposure for other tissues. Are the discussions on the various biomarkers adequate to elucidate their role in assessing human health effects from Pb exposure? Also, as the results from prospective cohort studies of Pb exposure have become available, our understanding of the optimal exposure metric to use in modeling specific health endpoints has evolved (*e.g.*, initially peak blood Pb levels were favored for child IQ, but that position now appears to be shifting toward concurrent or lifetime-

averaged blood Pb levels). Does Chapter 6 adequately address this issue of which exposure metrics are now believed to be most strongly associated with specific health endpoints and, therefore, should be the focus of exposure and risk assessments targeting those endpoints?

Charge Questions F2a. Newly-available human epidemiologic studies provide evidence for slowed physical and neurobehavioral development being associated with blood Pb levels ranging well below 10 μg/dL, and possibly to as low as 2 μg/dL. There is a focused discussion of one large pooled study that examined the association between blood Pb levels and IQ deficits in children from Boston, MA; Cincinnati, OH; Cleveland, OH; Rochester, NY; Mexico City, Mexico; Port Pirie, Australia; and Kosovo, Yugoslavia. The individual studies, which cover a wide range of exposure and outcome values, generally found negative associations between blood Pb levels and IQ. The pooled analysis shows a significant negative Pb effect on IQ measured at school age, after adjusting for common confounders. Due to the log-linear relationship, the slope of the Pb effect on IQ was greatest at the lower blood Pb level range, *i.e.*, below 10 μg/dL. Does this chapter adequately address questions regarding significant neurotoxic effects observed at low blood Pb levels (<10 μg/dL)? Also, is the issue of the influence of model selection on the estimated health effects adequately discussed?

Charge Questions F2b. In addition to other neurotoxic effects of Pb (*e.g.*, disturbances in behavior, mood, and social conduct; neuromotor function; and brain anatomical development and activity), other important Pb effects involving the renal system, cardiovascular system, reproductive and developmental system, immune system, and various other organ systems are discussed in Chapter 6. The genotoxic and carcinogenic potential of lead is also discussed. Does this chapter provide an adequate overview of key Pb health effects of concern? Are the key summary statements and conclusions regarding the effects of Pb on various organ systems sufficiently substantiated by the assessed epidemiologic evidence?

Charge Question F2c. Recent studies have observed significant effects on various health outcomes at relatively low lead levels. Examples include effects of lead on IQ, blood pressure, and early biomarkers of preclinical renal damage. However, there is concern as to what level of change for various health endpoints may be considered adverse or clinically significant on an individual or population basis. What are the views of the Panel regarding this issue?

Charge Questions F2d. Drawing causal inferences between increased Pb exposure and adverse health effects in epidemiologic studies is complicated by the presence of many potential confounders that may both affect Pb exposure and be associated with the health outcome of interest. Examples of potential confounders for Pb health effects include socioeconomic status, maternal IQ, maternal smoking, alcohol use, birth weight, and many others depending on the health outcome. In this chapter, is the discussion of the various potential confounders of Pb health effects adequate? Given the concern regarding the influence of such confounders on the effect estimates, are the stated key conclusions regarding Pb effects on various health outcomes appropriate?

Charge Questions F3. Discussions of epidemiologic studies mainly focus on studies of potential Pb effects among infants, school-aged children, the general population, and occupationally-exposed populations. Some studies also examined potentially susceptible individuals such as those with chronic medical diseases and specific genetic polymorphisms. Does Chapter 6 adequately cover key populations that should be considered for present purposes? Are the discussions of differences in individual vulnerability and susceptibility adequate?

G. Integrated Synthesis (Chapter 7).

Due to time constraints, NCEA staff did not attempt to craft an Integrative Synthesis (Chapter 7). At this time, CASAC Panel suggestions as to the format and content of this chapter would be welcomed. Such input would allow NCEA staff to focus on those points of greatest importance for inclusion in the next (2nd) Draft Lead AQCD.

H. Characterization of Pb-Related Welfare Effects (Chapter 8).

1. Terrestrial Ecosystem Effects. Sections 8.1.1 through 8.1.6 present new information on relevant measurement methods and the distribution of Pb in ecosystems and its effects on terrestrial species and ecosystems. Section 8.1.1 is intended to serve as the main body of the terrestrial effects portion of Chapter 8, while the other sections will ultimately serve as annexes to Chapter 8, similar to the format used for the Ozone AQCD. Thus, the initial perceived redundancy between Section 8.1.1 and the other sections in the chapter will be resolved later in preparing the Second Draft Lead AQCD.

Charge Questions H1: Do the subject sections adequately cover the most current (since 1996) information on the measurement methods, distribution, and effects of Pb on terrestrial ecosystems? Is there important material that was missed that should be covered in the next draft of the chapter?

2. Aquatic Ecosystem Effects. Sections 8.2.1 through 8.2.6 present new information on the measurement methods, distribution, and effects of Pb on aquatic species and ecosystems. Section 8.2.1 is intended to serve as the main body of the aquatics effects portion of Chapter 8, while the other sections will serve as annexes to Chapter 8, similar to the format used for the Ozone AQCD. Thus, the initial redundancy between Section 8.2.1 and the other sections in the chapter will be resolved in the Second Draft Lead AQCD.

Charge Questions H2: Do the subject sections adequately cover the most current (since 1996) available information on the measurement methods, distribution, and effects of Pb on aquatic ecosystems? Is there any important additional material that should be covered in the next draft of the chapter?

3. Critical Loads for Pb in Aquatic and Terrestrial Ecosystems. Sections 8.3 presents the latest information on the application of a "critical loads" approach for protecting aquatic and terrestrial ecosystems from the detrimental effects of atmospherically-delivered Pb.

Charge Questions H3: Does the subject section adequately cover the most current (since 1996) information on the potential use of critical loads? Is there important additional material that should be covered in the next draft of the chapter?

Appendix D – Review Comments from Individual CASAC Lead Review Panel Members

This appendix contains the preliminary and/or final written review comments of the individual members of the Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel who submitted such comments electronically. The comments are included here to provide both a full perspective and a range of individual views expressed by Panel members during the review process. These comments do not represent the views of the CASAC Lead Review Panel, the CASAC, the EPA Science Advisory Board, or the EPA itself. The views of the CASAC Lead Review Panel and the CASAC as a whole are contained in the text of the report to which this appendix is attached. Panelists providing review comments are listed on the next page, and their individual comments follow.

Panelist **Page #**

Dr. Joshua Cohen

Comments – Chapter 4
Joshua Cohen
February 18, 2006

Section 4.1

The introduction in Section 4.1 is generally good, although there are several passages that are slightly inaccurate and should be revised. Substantively, the biggest problem with this section is that it does not clearly explain the advantages and disadvantages of the two categories of modeling – mechanistic modeling and regression modeling – for quantifying the relationship between environmental lead levels and lead body burden (in particular, blood lead levels). EPA must develop and present a more compelling argument the advantages of mechanistic models. One advantage is that mechanistic models can be adjusted so that they can be used in contexts in different contexts. For example, they can be adapted to account for differences in lead bioavailability. They can also integrate multiple sources of exposure (e.g., lead in drinking water AND lead in soil). Those arguments are not made clearly in the existing text.

- Page 4-1, lines 1+ - The incorrectly asserts that a distinguishing characteristic between regression and mechanistic models is that regression models "can have relatively few parameters", whereas mechanistic models include more or all of the parameters needed to specify a relationship. Regression models can have many or few parameters, and the same is true of mechanistic models. I think that the main distinction is that regression models include only those quantities that can be measured and associated with measurements of the outcome of interest. For example, there are datasets that include residential soil lead measurements and corresponding child blood lead levels. As a result, it is possible to regress blood lead levels against soil lead levels to develop a statistical model. On the other hand, there is are no datasets that include both soil ingestion rates and blood lead levels. Hence, no regression model can be built relating blood lead levels and soil ingestion rates. The strength of regression models is that they are empirically verified (at least within the range of observation). Mechanistic models can incorporate quantities that have not been measured along with the outcome of interest, making it possible to characterize the impact of changes in those quantities on the outcome of interest. On the other hand, they are not directly verified empirically.
- Page 4-2, line 2: The term "Exposure-biokinetic" is incorrect in this context. "Exposure-intake" would be a better term because you are referring to models that represent "relationships between levels of lead in environmental media and human lead intakes."
- Page 4-2, line 7 – Likewise, the term "biokinetic model" in this context could be replaced with "intake-biokinetic model" because you are describing models that characterize the relationship "between lead intakes and levels of lead in body tissue". EPA can then go on to say that combining an exposure-intake model and an intake-biokinetic model results in an exposure-biokinetic model that quantifies the relationship between the amount of lead in environmental media and resulting lead concentrations in tissue.
- Page 4-2, lines 21-24 – The claim that mechanistic models "integrate complex information on lead exposure and biokinetics into a form that provides predictions, rather than just an organized grouping of observations" does not make sense. First, the statement does not make clear what the comparator is, although it appears to be

regression models. Second, regression models make predictions, so the statement appears to be incorrect.

- Page 4-3, line 6 – Consistency – Replace "exposure-biokinetics models" with "exposure-biokinetic models".

Section 4.2

No comments

Section 4.3

This section does a good job at describing the components of the IEUBK model (Section 4.3.1). The discussion of the model's calibration and evaluation (Section 4.3.2) is inadequate. Page 4-16, line 30-32 states that the IEUBK model has been evaluated by Hogan et al. (1998). It then goes on to describe the reasonable agreement that Hogan et al. reported between observed and IEUBK-predicted blood lead levels. EPA does not mention that another evaluation (Bowers and Mattuck, 2001) that found that "the IEUBK Model reproduces blood lead levels in children well for some communities, but poorly for others" (p. 1706). EPA does mention this paper (p. 4-17, line 17) but only in the context of stating that empirical comparisons have shown that numerous factors influence agreement between the model and observed blood lead values. EPA does not mention that, at least according to Bowers and Mattuck, these factors can be so idiosyncratic that it is impossible to account for them unless empirical blood lead measurements are available for the community in question (p. 1708), something that would obviate use of the model.

Even if the IEUBK model predicts GM blood lead levels without bias, I am concerned about the way in which the model is used to predict the probability that a child's blood lead level will exceed a specified level of concern (in particular, 10 ug/dL). Because the model's predictions are imperfectly correlated with actual blood lead levels, its low predictions will tend to be underestimates, while its high predictions will tend to be overestimates. It follows that the model will overpredict the probability that blood lead levels will exceed a specified level of concern at higher levels of environmental lead exposure (and likewise underpredict this probability at lower levels of environmental lead exposure). Even if the residual GSD (as estimated by Griffin *et. al.* (1999b) is reasonably correct), and hence the aggregate predicted risk of exceeding 10 ug/dL is close to observed values (i.e., summed over all individuals in the population), the model will tend to overestimate this risk at higher levels of environmental lead exposure (and underestimate it at lower levels of environmental lead exposure). These discrepancies can have ramifications for the use of such models to identify appropriate regulatory limits for exposure to lead.

Section 4.4

No comments.

Section 4.5

No comments.

Section 4.6

- Page 4-31, line 13 – Does EPA mean "arithmetic average" or geometric mean here? Please specify the intended modifier.
- Page 4-32, lines 26-27 – EPA states that "To the extent that model validation evaluations have indicated reasonably good matches between IEUBK or Leggett model outputs and empirical observations, the same can be reasonably expected for the AALM." I do not see how this claim follows. It is my understanding that the AALM can be thought of as

using the IEUBK model exposure module together with the Leggett model biokinetics. Section 4.3 of this chapter describes how the IEUBK model's predictions are consistent with observed blood lead levels. On p 4-38, EPA notes that the relationship between predicted blood lead levels and lead uptake is more than twice as steep for the Leggett model (0.88 ug/dL per ug/day uptake) as it is for the IEUBK model (0.36 ug/dL per ug/day uptake). That difference (see also Figure 4-13) implies that the blood lead levels predicted by the AALM will be substantially higher than the blood lead levels predicted by the IEUBK model. Why does EPA believe the AALM will produce valid blood lead level estimates given these differences between the Leggett and the heavily tested and validated IEUBK model?

Section 4.7

No comments.

Section 4.8

No comments.

Section 4.9

- Page 4-42, lines 5-7. The suggestion that remaining differences between the major models are "minor discrepancies" does not seem appropriate. As noted above, the impact of lead uptake on blood lead levels predicted by the Leggett model (and hence the AALM) exceeds the corresponding IEUBK model prediction by a factor of two.
- Page 4-42, lines 20+. EPA states that "While this magnitude of difference [a factor of approximately 2] may be substantial in the context of regulatory use of the models (e.g., for establishing cleanup goals at hazardous waste sites), it represents a remarkable convergence of various approaches taken to reduce the complex biokinetics of lead to tractable, and relatively simple, mathematical expressions." It may in fact be true that this degree of agreement between the m models is remarkable from a scientific perspective. However, EPA's purpose in studying and developing these models has been to aid regulatory efforts. The importance of these differences should therefore not be downplayed.
- Page 4-42, lines 24-28. Given that the Leggett and IEUBK models appear to differ substantially, it is difficult to see how the AALM model's predictions will simultaneously converge with those of both of these models.

Dr. Deborah Cory-Slechta

Air Quality Criteria Document
Chapter 5 Comments
Deborah Cory-Slechta

General Comments

1. Statements about the non-linear effects of Pb should probably be summarized, particularly with similar effects now being described for IQ and low blood Pbs, e.g.,

p. 5-11, lines 24-26.
pp. 5-20 line 30 through p. 5-21.
p. 5-28, lines 1-9, and figure. Particularly important given the non-linearity emerging with IQ
p. 5-29, lines 15-17
p. 5-131 lines 18-20 relating to hypertension

The delineation of components in Chapter 5 is peculiar. The experimental literature is followed by a rather strange configurations of topics, most of which seem to belong more appropriately in Chapter 6. Particularly confusing is the section on dose-response (p 5-66 onwards) said to be there to bridge the gap between the findings in 5.3.1 and those to be discussed in section 6. The presentation of information in Figures 5 and 6 and what is included in each of these two chapters needs to be reconsidered.

Specific Comments

5-2, lines 20-23 - Logic doesn't follow

5-4, line 4 – Furthermore…was not observed. Seems a non sequitur since accumulation was not previously referred to.

5-5, line 2 – interfacial?

Line 7 – 100 ug/100 ml should be changed to µg/dL as it is other places in the document; this should be corrected throughout since it is inconsistent. The most standard use, µg/dL should be adopted.

5-19, lines 2-3. Why is this approach said to be of little value? Seems a judgment out of context, or in hindsight, and dismissive in a broad context.

5-19, line 6 – the most reliable evidence? In who's judgment? Why so?

5-19, line 11 – Says this was the significant advance in the field. Again, by who's judgment? Also contradictory, since there has just been criticism of the low relevance of in vitro approaches. Not clear how such conclusions were reached; they should be deleted and are not necessary for the document.

5-20, lines 1-2, drawn the most attention? By what criteria?

5-22, lines 23-24, it is critical to point out the dangers of measuring a few parameters of a neurochemical system, finding that they all change, and assuming that they are related. It is likely that there were changes in other neurotransmitter systems as well that could also have been correlated with behavioral changes. Unless experiments are explicitly carried out to examine the nature of the relationship, these interpretations can be misleading.

5-23, lines 1-10. This interpretation seems inconsistent with the findings. Specifically, an increase in NMDA receptors would seem to suggest that the system sees inadequate agonist and therefore an up-regulation occurs, while the decrease in MK-801 binding would suggest that the binding sight sees an excess of antagonist and down-regulates in response to this. Indeed, the study of Lasley and Gilbert (1996), Gilbert et al. (1996) found decreased stimulated release of glutamate in hippocampus. There is of course a great danger in trying to engender unitary effects of Pb; it seems clear that the outcome can change greatly depending upon the timing, level and chronicity of exposure, and therefore one size fits all may not be realistic, nor should it be suggested that it should be the case.

5-25, lines 26-27. The interpretation is not supported by any data; what studies directly show that nicotinic cholinergic changes play a role in Pb-induced cognitive deficits?

p. 5-26, line 13, why is this one of the 'most significant' advances? Its one more line of evidence, supporting what has already been shown in a functional capacity.

5-31, line 11, pathology, not function

5-33 through 5-34 really is abbreviated relative to what is described in excruciating detail at the biochemical level; this seems particularly odd given that the levels of concern are based on cognitive and behavioral deficits

5-34 through 5-35 same story with rodents; contradictory findings are presented within rodent studies and contradictory to non-human primate; these are not evaluated in any depth. This section is missing numerous studies related to the whole area of attention; there are contradictory findings on sustained attention; the work by Morgan et al. 2001 shows a trivial effect that required 20 animals per group. The work by Brockel et al fails to support it and in fact demonstrates the importance of delay of reward. None of this work is included. These studies are particularly important as they relate to the behavioral mechanisms underlying cognitive deficits and no doubt relate to the changes observed in IQ.

5-35 through 5-36 Not clear why the work of interactions of Pb and cocaine is described as producing scientifically important results? This is not at all surprising given the well known effects of Pb on dopaminergic systems, particularly the mesocorticolimbic system.

5-36 There are numerous other studies using drug discrimination to evaluate dopaminergic function in Pb-treated rats, none of which are noted or described.

5-39 lines 12-14 Again, there is no real presentation of the attention work that has been done; deficiencies in sustained attention are not well demonstrated behaviorally and stronger studies documenting problems with delay of reward by Brockel et al. are not presented. In general, the summary on this page does not really capture the understanding from the experimental literature on behavioral changes.

5-41 to 5-42 mentions the half life of Pb elimination from brain, only citing unpublished alterations. There are several other published studies, including one that has examined the issue on a regional basis in brain that are more appropriate to cite here; they provide half-lives that are longer than that indicated in an unpublished (non-peer reviewed) study.

5-43, summary, lines 1-6 seems a gross overgeneralization of the literature and by no means anything demonstrated, especially since all of the neurotransmitters exist within the mesocorticolimbic circuitry that is critical to executive functions.

5-43, lines 18-20 makes little sense. Why wouldn't there be susceptibility factors? For example, gender, we know there are differences between males and females (e.g., Cory-Slechta et al., 2004) and these have received no attention in the literature (even though we also know that males and females exhibit different PbBs). Why wouldn't we expect polymorphisms to interact with Pb. And certainly period of exposure is a susceptibility factor.

5-43 and prior – there is no mention of the possibility of fetal programming with Pb. Recent findings by Cory-Slechta et al. (2004) and by Zawia et al. (ref) definitely speak to the possibility of permanent effects on important systems and proteins need to be identified, particularly as they invoke an etiological role for Pb in many other disorders and diseases. Also, never really describes what effect levels are in animals; says 15 and above, but there are studies documenting effects below 15 and below 10; it is important to note these given the emerging literature on children and IQ.

5-44 to 5-45 discussion of biomarkers. This seems quite distorted, what are typically known as susceptibility factors are somehow here renamed as biomarkers of susceptibility. This makes little sense and isn't consistent with what are typically deemed biomarkers. Also, the issue of biomarkers as selective or specific to Pb are never mentioned

5-46 lines 7-16; unclear why these changes in peripheral 5-HIAA and HVA are listed as biomarkers. Not clear what these mean of if they are at all specific to Pb exposure.

5-46, line 18 clinically 'oriented'? Just call these effects. This is a tautology when saying biomarkers of effect.

5-51 lines 1-23 are really tangential here and reads more like a textbook than a criteria document; this should be shortened or eliminated.

5-51 lines 24-31 are repetitive of what has already been said.

5-52 lines 1-10, again read like a textbook and add nothing.

5-53, line 9-10 unclear what is meant here, does it mean that the presumption was that there should have been a relationship and there wasn't?

5-53 lines 20-21 same as lines 9-10; shouldn't the null hypothesis be no relationship?

5-54, lines 20-22 also give support to an absence of an objective basis of comparison of studies here; they seem to presume that there has to be a relationship, thus only studies supporting it are defined as "compelling".

5-58 lines 5-26 describes a study that doesn't even include PbBs and imparts Pb effects to differential IQs in suburban vs. urban Detroit. This is a highly inappropriate inclusion in this criteria document and should be deleted.

5-62 lines 4-7 again, a finding that seems to be considered negative since it doesn't show the positive relationship the author apparently wants to support. It seems critical for a criteria document in particular to be based on the null hypothesis.

5-64, line 22, halotypes should be haplotypes

5-66; this section seems out of place. It is not critically presented. For example, how was the calculation of .48uM as the in vitro equivalent of 10 µg/dL blood Pb determined? States that almost all of the Pb in a 'neurochemistry experimental system' (whatever that is) can participate in a reaction…this completely ignores precipitation and binding of Pb in these assays.

5-67 lines 1-10; this argument is unclear and not presented in a critical way. The data for a half life of 2 years for Pb in brain cites a study of modeling and is not consistent with what has been described in experimental studies. The fact that plasma Pb is not the dose to brain seems to make little sense. The plasma compartment would remain a source of Pb if blood Pb remains elevated. What human data can be cited to support the 2 year brain half life?

5-67 lines 21-26 This is total conjecture, unsupported by data and should be deleted; the entire section on dose-response is hypothetical and should not be included in the criteria document.

5-68 lines 1-11 Again, confusing and unsupported by any substantial data. The section should be deleted.

5-68 lines 14 through 20; not clear what the point is here. Very confusing sentences.

5-68 through 5-70 Not clear why this section is included here instead of in the chapter on epidemiology where these effects are described. Moreover, the conclusions that are presented here are flawed (5-70, lines 9-24). These approaches, while they certainly on a group basis, help to more specifically delineate the basis of the IQ deficits reported, will not be able to provide a specific link to lead, i.e., to demonstrate that a lower performance capability can be attributed to Pb.

5-73, lines 18-20 again fail to be based on a null hypothesis.

5-75, lines 9-11, again, failure to assume the null hypothesis; any lack of a relationship is always presumed to be due to some other source of variability.

5-75 and 5-76 on SES; this is really demographic data and should be included in sections of the document describing demographics; the same can be said for the preceding section on children and SES. The same can be said for sections on nutritional status since these are really co-variates in the populations and not describing health outcomes.

5-77 lines 15-17; again, failure to assume the null hypothesis; moreover, the putative explanation for the absence of an effect of calcium here is inconsistent within the sentence: high lead burdens, but blood Pbs of 8.5 µg/dl.

5-86 lines 1-2; need to elaborate the evidence for the adaptation. What is it?

5-86 line 16-17 missing the word "in" after gross changes.

5-88 lines 1-10; blood Pb values of 35-40 µg/dl can hardly be considered lower levels of exposure

5-102 lines 13 through 20; the Cory-Slechta paper shows main effects in both males and females and no interactions, so developmental only Pb exposure produces fetal glucocorticoid programming.

5-105 through 5-108 conclusions seems like a restatement of all that preceded it rather than conclusions; perhaps bullet points here would be preferable.

5-111, line 8, change 'administrating' to 'administering'

5-163 lines 13-21 cites the study of Sanchez-Fructuoso et al. (2002) and states that "The authors emphasized that there was no redistribution to brain. Cory-Slechta et al. (1987) had originally reported that with $CaNa_2EDTA$ chelation in rats Pb is preferentially mobilized from bone and then redistributed to other organs including brain. The Sanchez-Fructuoso et al. (2002a,b) findings stand in contrast…" In fact, that is not the case; the redistribution of Pb to brain reported by Cory-Slechta et al. (1987) occurred in response to a single injection of $CaNa_2EDTA$, and indeed with further injections of $CaNa_2EDTA$, levels of Pb in brain ultimately declined. The protocol used by Sanchez-Fructuoso et al. (2002) never examined effects in response to a single $CaNa_2EDTA$ injection. Levels of Pb in brain were only examined after 3 courses of 5 $CaNa_2EDTA$ treatments. Thus, this is not a failure to replicate as the text suggests.

Pages 5-178 to 5-183 There is a study by Meja et al. (Neurotoxicology and Teratology, 1997, vol. 6:489-497) examining combined effects of Pb and As that reports that Pb levels in brain are increased by this co-exposure.

5-214 line 2, change 'neurological' to 'nervous.'

5-215 to 5-218 This introduction to the immune system should be deleted; no such section is presented for any other target organ.

Dr. Ellis Cowling

Dr. Ellis Cowling
North Carolina State University
March 10, 2006

Review of the Air Quality Criteria for Lead (First External Review Draft)

General Comments on the Organization, Format, and Content of Air Quality Criteria Documents and their Relationship to Staff Papers

This past year has provided an unusual opportunity for CASAC, NCEA, and OAQPS to work together in efforts to further optimize the design and organization of Air Quality Criteria Documents and Staff Papers. During this one year, in rather rapid succession, CASAC has reviewed both planning documents, and review drafts of both criteria documents and staff papers for three of the five pollutants presently recognized criteria pollutants. In each case, CASAC has been presented with very large documents that require very careful attention from the standpoint of many different scientific disciplines in order to summarize the present state of scientific understanding about:

1) the chemistry and physics of the pollutant itself,
2) the sources of air emissions of the pollutant or its precursors,
3) the transport. transformation, and atmospheric deposition processes by which the pollutant is delivered to sensitive receptors,
4) the nature and magnitude of the effects of the pollutant on both human health and on human welfare, and
5) the establishment of science- based national ambient air quality standards that in the judgment of the Administrator of EPA will be useful and effective in decreasing exposures and therefore decreasing the magnitude and prevalence of adverse effects on both human health and human welfare with an "adequate margin of safety" at lest in the case of effects on public health, and finally
6) the continuously evolving historical development of both scientific understanding about all five of these preceding aspects of the pollutant, its health and environmental effects, and the art and practice of its management over time.

The laws of our country require that this difficult and challenging intellectual work should be accomplished periodically (ideally every five years) by scientists, engineers, policy analysts, and decision makers who are charged by our society to do their respective parts -- leading to scientifically sound, policy effective, and socially acceptable decisions in a contentious democratic society that often is resistant to change and frequently uses the courts of our country to set demanding deadlines for the development of Criteria Documents, Staff Papers, and the promulgation and implementation of Regulations and Rules for air quality management.

During the past year CASAC Members and Panelists have reviewed and offered our carefully considered individual and collective advice and counsel about the adequacy of the

criteria documents, staff papers, and the proposed rules and regulations for ozone and other photochemical oxidants, fine and coarse particulate matter, and now lead.

In all three of these cases, CASAC has done its best to review the documents prepared by NCEA and OAQPS and to offer our individual and collective counsel and advice about the scientific content, organization, and the scientific objectivity and tone of impartiality of these very large criteria documents.

Beginning in the case of the Criteria Document and Staff Paper for Ozone and Related Photochemical Oxidants, a somewhat different organizational structure was used by NCEA.

The new organizational format called for relatively brief Main Chapters that consist of two parts:

1) a concise summary of "Key findings/conclusions" from earlier assessment documents, and
2) carefully prepared descriptions of advances in scientific understanding that have been developed since the time of the last review and published in more recent scientific literature.

The new structure also calls for development of very detailed Annexes for each Main Chapter in which many important advances in scientific understanding are presented in much more thorough fashion than in the corresponding Main Chapter.

The final features of the new structure and organization of Air Quality Criteria Documents were development of both an Integrative Summary Chapter and an Executive Summary for the whole Criteria Document. The purpose of these two additional parts of the Criteria Document was to draw together the major findings and conclusions of scientific understanding developed within each of the Main Chapters and corresponding Annexes and to to present in an integrative way the Key Findings and Conclusions (from both earlier assessment reports and the most recent description of scientific advances) and thus provide a maximally useful foundation for the Staff Paper.

In the words of OAQPS, the purpose of the Staff Paper is to:

> "provide a critical assessment of the latest available scientific information upon which the National Ambient Air Quality Standards are to be based. Drawing upon the AQCD, staff in EPA's Office of Air Quality planning and Standards (OAQPS) within the Office of Air and Radiation prepares a Staff Paper that evaluates policy implications of the key studies and scientific information contained in the AQCD and presents the conclusions and recommendations of the staff for standard setting options for the EPA Administrator to consider. The Staff Paper is intended to 'bridge the gap' between the scientific assessments contained in the AQCD and the judgments required of the Administrator in determining whether it is appropriate to retain or to revise the primary and secondary NAAQS."

Many members of CASAC were very pleased with the good sense of the revised structure and format of Criteria Documents. We are convinced that these innovations in the overarching method of organization of Criteria Documents will better serve the interests of the wide variety of audiences that are interested to learn more about scientific understanding of each of the criteria pollutants and their effects on both human health and welfare. Thus, many of us believe that these innovations in structure should be retained and used not only in preparing the Second

External Review Draft of the Criteria Document for Lead but also in preparing other Criteria Documents for other Criteria Pollutants.

In doing so, it is of course important that the different target audiences for the Executive Summary, the Main Chapters of the Criteria Document itself, and the various Annexes be very well defined and well understood by all of the staff, consultants, and editors that prepare these three different treatments of the same body of scientific knowledge.

It is even more imperative that the scientific content, objectivity, and tone of impartiality of the Executive Summary and the Integrative Summary Chapter of the Criteria Document [and the Staff Paper as well!] be consistent not only with the scientific content, objectivity, and tone of impartiality of the Main Chapters of the Criteria Document itself, but also with the scientific content and objectivity of the more detailed Annexes. Differences in content of these different parts of the same Criteria Document [and the related parts of the Staff Paper] should be based primarily on their relevancy to their respective purposes and target audiences. Discrepancies in scientific content, objectivity, and tone of impartiality in these distinct parts of the Criteria Document and Staff Paper will inevitably lead to decreased confidence in the validity and reliability of the different parts of both types of documents. Thus such discrepancies must be carefully avoided. This will require a larger degree of common understanding among authors, consultants, editors, and managers of the Criteria Document and Staff Paper development processes than many members and Panelists within CASAC believe has been achieved to date.

A useful mechanism for ensuring that there is an effective and concise summary of "Key Findings and Conclusions" in each Main Chapter is to require that an Executive Summary be prepared for each Main Chapter and that these statement of Key Findings and Conclusions from individual Main Chapters be used in constructing both the Executive Summary for the whole Criteria Document and in developing the organizational framework for the Integrative Summary Chapter.

One suggestion for avoiding discrepancies in communication among these several different parts of Criteria Documents is to require that the same carefully-crafted summary statements of scientific findings and conclusions are not only included (**but also printed in bold-face type**) within <u>all parts</u> of complex scientific assessment documents. This editorial device is used in many high-quality National Research Council assessment reports that also deal with very complex policy relevant scientific issues.

In written comments on the Criteria Document for Ozone and Other Photochemical Oxidants dated December 2, 2005 I recommended [and affirm here once again] that all authors, consultants, editors, and managers engaged in the preparation of Criteria Documents and EPA Staff Papers take full advantage of- and use the attached published "*Guidelines for the Formulation of Statements of Scientific Findings to be Used for Policy Purposes.*"

These guidelines, written in the form of checklist questions, were developed by the members of the Oversight Review Board (ORB) of the National Acid Precipitation Assessment Program to assist scientists, engineers, and policy analysts dealing with other environmental research and assessment programs in formulating statements of scientific findings to be used in policy decision processes. The distinguished members of the ORB who prepared these guidelines included: Milton Russell, former Assistant Administrator for EPA, Chauncey Starr, former Director of Research for the Electric Power Research Institute (EPRI), Tom Malone, former

Foreign Secretary for the National Academy of Sciences, John Tukey, Distinguished Professor of Statistics at Princeton University, and Kenneth Starr, Nobel Prize Winner in Economics.

GUIDELINES FOR FORMULATION OF STATEMENTS OF SCIENTIFIC FINDINGS TO BE USED FOR POLICY PURPOSES

The following guidelines in the form of checklist questions were developed by the NAPAP Oversight Review Board to assist scientists in formulating presentations of research results to be used in policy decision processes.

1) **IS THE STATEMENT SOUND?** Have the central issues been clearly identified? Does each statement contain the distilled essence of present scientific and technical understanding of the phenomenon or process to which it applies? Is the statement consistent with all relevant evidence that is available in the published literature. Is the statement contradicted by any important evidence in the published literature? Have apparent contradictions or interpretations of available evidence been considered in formulating the statement of principal findings?

2) **IS THE STATEMENT DIRECTIONAL AND, WHERE APPROPRIATE, QUANTITATIVE?** Does the statement correctly quantify both the direction and magnitude of trends and relationships in the phenomenon or process to which the statement is relevant? When possible, is a range of uncertainty given for each quantitative result? Have various sources of uncertainty been identified and quantified, for example, does the statement include or acknowledge errors in actual measurements, standard errors of estimate, possible biases in the availability of data, extrapolation of results beyond the mathematical, geographical, or temporal relevancy of available information, etc. In short, are there numbers in the statement? Are the numbers correct? Are the numbers relevant to the general meaning of the statement?

3) **IS THE DEGREE OF CERTAINTY OR UNCERTAINTY OF THE STATEMENT INDICATED CLEARLY?** Have appropriate statistical tests been applied to the data used in drawing the conclusion set forth in the statement? If the statement is based on a mathematical or novel conceptual model, has the model or concept been validated? Does the statement describe the model or concept on which it is based and the degree of validity of that model or concept?

4) **IS THE STATEMENT CORRECT WITHOUT QUALIFICATION?** Are there limitations of time, space, or other special circumstances in which the statement is true? If the statement is true only in some circumstances, are these limitations described adequately and briefly?

5) **IS THE STATEMENT CLEAR AND UNAMBIGUOUS?** Are the words and phrases used in the statement understandable by the decision makers of our society? Is the statement free of specialized jargon? Will too many people misunderstand its meaning?

6) **IS THE STATEMENT AS CONCISE AS IT CAN BE MADE WITHOUT RISK OF MISUNDERSTANDING?** Are there any excess words, phrases, or ideas in the statement which are not necessary to communicate the meaning of the statement? Are there so many caveats in the statement that the statement itself is trivial, confusing, or ambiguous?

7) **IS THE STATEMENT FREE OF SCIENTIFIC OR OTHER BIASES OR IMPLICATIONS OF SOCIETAL VALUE JUDGMENTS?** Is the statement free of influence by specific schools of scientific thought? Is the statement also free of words, phrases, or concepts that have political, economic, ideological, religious, moral, or other personal-, agency-, or organization-specific values, overtones, or implications? Does the choice of how the statement is expressed rather than its specific words suggest underlying biases or value judgments? Is the tone impartial and free of special pleading? If societal value judgments have been discussed, have these judgments been identified as such and described both clearly and objectively?

8) **HAVE SOCIETAL IMPLICATIONS BEEN DESCRIBED OBJECTIVELY?** Consideration of alternative courses of action and their consequences inherently involves judgments of their feasibility and the importance of effects. For this reason, it is important to ask if a reasonable range of alternative policies or courses of action have been evaluated? Have societal implications of alternative courses of action been stated in the following general form?:

"If this [particular option] were adopted then that [particular outcome] would be expected."

9) **HAVE THE PROFESSIONAL BIASES OF AUTHORS AND REVIEWERS BEEN DESCRIBED OPENLY?** Acknowledgment of potential sources of bias is important so that readers can judge for themselves the credibility of reports and assessments.

More Specific Comments:

Target Audiences

During the CASAC meeting on the First External Review Draft of the Criteria Document on Lead on February 28-March 1, several Members and Panelists mentioned that the original 1977 Criteria Document on lead, the 1986 updated revision and its accompanying Addendum, and the 1990 Supplement to the Criteria Document on lead had been valuable sources of scientific background information (and even for inspiration and definition of career goals) for scientists and engineers in years past. Thus, in addition to the most immediate value of Criteria Documents and Staff Papers as background for decisions by the Administrator of EPA, there are a number of other target audiences which have in the past (and no doubt also in the future) will profit from the rigorous scientific reviewing and evaluation that is accomplished by these documents.

Thus, graduate students and post-doctoral fellows in universities, in other federal and state offices, leaders in industry, leaders in public interest groups and trade organizations, teachers of courses in universities, and members of the public at large should be recognized as target audiences. This wide array of target audiences should be recognized and borne in mind by all the authors, consultants, editors, and managers involved in the design, organization, preparation, evaluation, and response to reviewer comments concerning the information contained in both Criteria Documents and Staff Papers.

Multi-Media Nature of Lead

More than any other of the five Criteria Pollutants which CASAC has been charged to review in recent years, lead crosses more if not all of the "media of concern" to USEPA. These multi-media aspects include: 1) air emissions and deposition of lead from transportation vehicles, metal smelters, battery production and recycling facilities, 2) lead content of drinking water, 3) lead containing paints, 4) lead containing pesticides involved in food production, 5) soil contamination with lead, 6) lead in municipal and solid waste management, 7) lead contamination of superfund sites, etc. The multi-media nature of this pollutant is touched upon in several different parts of this the First External Review Draft. It may be worthwhile to draw these multi-media aspects of lead together in a single part of the Criteria Document, probably in Chapter 1.

Content and Placement of the Integrative Summary Chapter

Lack of an Integrative Summary Chapter and a comprehensive Executive Summary for the whole Criteria Document is a major shortcoming of the First External Review Draft. Although the original intent was to prepare an Integrative Summary Chapter (Chapter 7) that would deal only with effects of lead on public health, (and thus to include information only from Chapters 1-6), it clearly would be much more advantageous and appropriate for the Integrative Summary Chapter also to include Environmental Effects of Lead (Chapter 8) as well as effects of lead on public health.

This is especially desirable because it is historically deposited lead that is the principal object of current concern rather than current "ambient" air concentrations. Very substantial decreases in air concentrations and atmospheric deposition of lead into the environment have been achieved in recent decades. Thus, most current exposures of both people and living organisms in natural and managed ecosystems are caused primarily by redistribution of environmentally

persistent airborne lead compounds deposited in soils, sediments, and surface waters during earlier decades of the present century.

This more broad perspective can be achieved by reversing the chapter numbers for chapters 7 and 8 so that the Integrative Summary Chapter comes at the end of the Criteria Document and provides an integrative summary of both health and environmental effects of lead. A similarly broad perspective will be desirable in the design and content of the Executive Summary of the whole Criteria Document for lead.

Response to Specific Issues in Chapter 8

It was good to learn from Lester Grant's transmittal memo dated February 15, 2006 that the intent of Section 8.1.1 and 8.2.1 is to serve as the main body of the terrestrial effects and aquatic effects portions of Chapter 8, respectively, while the other sections (8.1.2 through 8.1.6 and 8.2.1 through 8.2.6) will ultimately serve as annexes to chapter 8, similar to the format used for the Criteria document on Ozone and Related Photochemical Oxidants. In this way the redundancy between Section 8.1.1 and Sections 8.1.2 through 8.1.6 regarding terrestrial effects, and between Section 8.2.1 and Sections 8.2.2 through 8.2.6 regarding aquatic effects will be resolved in the Second External Review Draft for Lead.

Charge Question H3 -- Discussion of the Concepts of Critical Loads

Many of us were especially pleased to see the relatively thorough discussion at the end of Chapter 8 regarding the alternative concepts of critical loads, critical limits, target loads, and target times that have been developed in European and Canadian scientific literature to guide the processes of decision making regarding both environmental and public health effects of airborne chemicals. Although these alternative concepts and processes of analysis of multiple pollutant/multiple effects have not been carefully considered for use in the United States, we believe, together with the authors of the National Research Council/National Academy of Sciences 2004 report on "Air Quality Management in the United States," that these alternatives should be considered very carefully as air quality management tools for use in this country as well.

Dr. Bruce Fowler

Bruce Fowler 3/10/06

Post - Meeting comments on EPA DRAFT CASAC and response to Chapter 5 Charge Questions

1. First – I would like to reaffirm that my pre- meeting comments regarding the need for strong editorial assistance in Chapter 5 with regard to organization and the need to put the relevant references on the brain and kidney lead binding proteins into their respective sections near the front of the chapter. These references are generally well captured and discussed in Section 5.11 but missing or covered in passing in the brain and kidney sections in those earlier sections. This is really an editorial matter.

2. If the recent work by Drs. Michael Waalkes / Robert Goyer and colleagues at NIEHS on MT and alpha Synuclein is published or in press by the time this EPA document is ready for publication, that should also be cited. The recent data presented at the SOT meeting seem to indicate that MT may be interacting with this protein as well.

3. I note that there were some references in the document to non-mammalian systems so I offer the following 2 references regarding lead-binding proteins in catfish and altered susceptibility to lead inhibition of liver ALAD in this species for completeness.

   Conner EA, Fowler BA. Preliminary purification and partial characterization studies of a low-molecular weight cytosolic lead-binding protein in liver of the channel catfish (Ictalurus punctatus). Aquatic Toxicology 28: 29-36, 1994.

   Conner EA, Fowler BA. Biological and immunological properties of Fish Hepatic δ-aminolevulinic acid dehydratase (Porphobilinogen synthetase). Aquatic Toxicology 28:37-52, 1994.

4. Interactions between lead and other toxic elements such as arsenic and cadmium. As discussed in the meeting, there are published data on additive interactions among lead cadmium and arsenic from Mahaffey and co-workers during the 1977-1981 time period, and I can forward these if needed. The more recent studies (in vivo and in vitro) from my lab group are preparation and will hopefully be submitted soon. I will forward them as they are accepted or in press. It is my opinion that interaction among these elements is important since they frequently occur together in Superfund sites and in aerosols from smelting or coal- fired power plants. The literature is limited so it should not be an onerous task to have an up to date summary in a short time period.

5. I agree with the other suggestions offered by Dr. Goyer.

Bruce Fowler Responses to Charge Question E1

E1a. I would suggest adding some references to lead binding proteins in brain since they are found in both animals and humans and appear to play an important intracellular role in mediating low dose lead bioavailability to other sensitive molecular processes in brain. They may also help to explain inter –individual differences in sensitivity to lead neurotoxicity. Some suggested references are as follows:

1. Oskarsson A, Squibb KS, Fowler BA. Intracellular binding of lead in the kidney: Partial isolation and characterization of post-mitochondrial supernatant lead-binding components. Biochem Biophys Res Commun 104:290-298, 1982.

2. Goering PL, Mistry P, Fowler BA. A high affinity lead-binding protein in brain attenuates lead inhibition of δ-aminolevulinic acid dehydratase: Comparison with a renal lead-binding protein. J Pharmacol Exper Therap 237:220-225, 1986.

3. DuVal GE, Fowler BA. Preliminary purification and characterization studies of a low molecular weight high affinity cytosolic lead-binding protein in rat brain. Biochem Biophys Res Comm 159:177-184, 1989.

4. Quintanilla-Vega B, Smith DR, Kahng MW, Hernandez JM, Albores A, Fowler BA. Lead-binding proteins in brain tissue of environmentally-lead exposed humans. Chem Biol Interact 98:193-209, 1995.

E1b. There is an extensive literature on bone and other calcified tissues as storage sites for lead but the basic scientific literature regarding permanent impact of lead on bone development is more limited. The work of JE Puzas and colleagues at the University of Rochester is perhaps the most recent relevant in this regard. Other suggested references regarding lead storage in bone and molecular effects are given below.

Suggested possible references:

1. Sauk J, Smith T, Silbergeld EK, Fowler BA, Somerman MJ. Lead inhibits secretion of ostenectin/SPARC without significantly altering collagen or Hsp47 production in osteoblast-like ROS 17/2/8 cells. Toxicol and Appl Pharmacol 116:240-247, 1992.

2. Todd AC, McNeill FE, Fowler BA. In vivo X-Ray fluorescence of lead in bone. Environmental Research 59: 326-335, 1992.

3. Silbergeld EK, Sauk J, Somerman M, Todd A, McNeil F, Fowler B, Fontaine A, van Buren J. Lead in bone: storage site, exposure source, and target organ. Neurotox 14(2-3):225-36, Summer-Fall 1993.

4. McNeill FE, Todd AC, Fowler BA, Laughlin NK. The in vivo measurement of bone lead stores by 109Cd K X-ray fluorescence in a non-human primate (Macaca mulatta). Basic Life Sci. 60:315-8, 1993.

5. McNeill FE, Laughlin NK, Todd AC, Sonawane BR, Van DeWal KM, Fowler BA. Geriatric bone lead metabolism in a female non-human primate population. Environ Research 72:131-139, 1997.

E1c. The cited animal studies regarding chelation / intervention are relevant to analogous studies in humans since similar biochemical/molecular principles are operating. The question of relevance may also be considered from the perspective of risk management for humans exposed to lead and if this is a concern for EPA, then it is appropriate to cover them in this document.

E1d. The newer findings regarding the interactions of lead with specific molecules, lead binding, transport kinetics and nucleotide pools are certainly useful information but more work is needed to in order to make the linkage to mechanisms underlying specific health endpoints. These parameters represent a number of possible molecular events that are in operation following exposure to lead. There are other factors such as changes in gene expression patterns and other compensatory mechanisms which may be of particular importance at low dose exposure levels. Some possible references for consideration relating to lead interactions with specific target molecules are listed below. These are offered as suggestions only.

Suggested possible references:

1. Goering PL, Fowler BA. Regulation of lead inhibition of δ-aminolevulinic dehydratase by a high affinity renal lead-binding protein . J Pharmacol Exp Therap 231:66-71, 1984.

2. Victery WW, Miller CR, Fowler BA. Lead accumulation by rat renal brush border membrane vesicles. J Pharmacol Exp Therap 231:589-596, 1984.

3. Mistry P, Lucier GW, Fowler BA. High affinity lead-binding proteins from rat kidney cytosol: Mediate cell-free nuclear translocation of lead. J Pharmacol Exp Therap 232:462-469, 1985.

4. Goering PL, Fowler BA. Mechanisms of renal lead-binding protein protection against lead-inhibition of δ-aminolevulinic acid dehydratase. J Pharmacol Exp Therap 234:365-371, 1985.

5. Oskarsson A, Fowler BA. Effects of lead inclusion on subcellular distribution of lead in rat kidney: The relationship to mitochondrial function. Exper Molec Pathol 43:409-417, 1985.

6. Oskarsson A, Fowler BA. Effects of lead on the heme biosynthetic pathway in rat kidney. Exper Molec Pathol 43:397-408, 1985.

7. Mistry P, Mastri C, Fowler BA. Influence of metal ions on renal cytosolic lead-binding proteins and nuclear uptake of lead in the kidney. Biochem Pharmacol 35:711-713, 1986.

8. Goering PL, Mistry P, Fowler BA. A high affinity lead-binding protein in brain attenuates lead inhibition of δ-aminolevulinic acid dehydratase: Comparison with a renal lead-binding protein. J Pharmacol Exper Therap 237:220-225, 1986.

9. Goering PL, Fowler BA. Mechanism of kidney metallothionein reversal of lead inhibition of δ-aminolevulinic acid dehydratase. Arch Biochem Biophys 253:48-55, 1987.

10. Goering PL, Fowler BA. Metal constitution of metallothionein influences inhibition of δ-aminolevulinic acid dehydratase (porphobilinogen synthase) by lead. Biochem J 245:339-345, 1987.

11. Fowler BA, Kahng MW, Smith DR, Conner EA, Laughlin NK. Implications of lead- binding proteins for risk assessment of lead exposure. J Exposure Analysis and Environ Epidemiol 3: 441-448, 1993.

12. Smith DR, Kahng MW, Quintanilla-Vega B, Fowler BA. High affinity renal lead-binding proteins in environmentally exposed humans. Chem Biol Interact 115:39-52, 1998.

E.1e. The oxidative stress theory does represent a plausible general mechanism of action that is likely to occur across organs and species. The degree to which it may have an impact will depend upon a number of other factors such as anti-oxidative stress mechanisms (e.g., GSH, metallothionein), cellular repair mechanisms such as the stress proteins, duration of exposure and nutritional status and concomitant exposure to other oxidative stress inducing agents such as arsenic and cadmium. Does EPA wish to take up the issue of interactions with other toxic metal s/metalloids commonly found with lead in this document as well as compensatory mechanisms against oxidative stress? Please see comments and reference below on oxidative stress from combined exposures.

E1f. The issue of animal – human and apparent dose differences between species is a long-standing concern for the risk assessment of many chemicals. Perhaps a better way to look at the problem is to consider dosages at the molecular or target cell levels of biological organization. Dosage at the target cell level may be more relevant to risk than trying to use administered or intact organism exposure levels for such purposes. As scientific understanding of what doses of lead, in this case, cause biological disruption of critical target or cellular pathways increases confidence in such an approach would also increase. The potential confounding scientific variables then become changes in lead kinetics as a function of dose and time as well as the influence of compensatory molecular mechanisms which appear to be operational at low dose exposure levels. The issue of populations at special risk as a function of age, gender, nutritional status and genetic predisposition would also complicate the selection of a specific cut –off value. A probabilistic approach may prove to be more satisfactory in the long run for estimating a cut-off range.

One suggested reference regarding exposure to lead, cadmium and arsenic at LOEL doses levels that may be useful to this discussion is given below. A series of full papers with both in vitro and in vivo studies is in preparation by my former students.

1. Fowler BA, Whittaker MH, Lipsky M, Wang G, Chen XQ. Oxidative stress induced by lead, cadmium and arsenic mixtures: 30-day, 90-day, and 180-day drinking water studies in rats: an overview. Biometals 17(5): 567-8, 2004.

Dr. Andrew Friedland

Andy Friedland, Dartmouth College
26 February 2006

Preliminary Comments on First External Review Draft Lead Air Quality Criteria Document (Dated December 2005) with a specific focus on Chapter 8: Environmental Effects of Lead

Charge Question A1:

The document format is certainly useful. The subject of historical trends in atmospheric emissions, and the history of deposition of Pb at specific locations over time occur repeatedly throughout the document. Within Chapter 8, there are a number of locations where atmospheric deposition is discussed and the history of the adding of alkyl-Pb and then elimination of additives is described. Chapter 2 also contains some discussion of sources of Pb and subsequent atmospheric transport. I have not yet read other chapters closely, but it appears that history of Pb deposition occurs elsewhere in the document. It would be useful to discuss as a group the clearest, most consistent and most efficient way to present historical trends in atmospheric emissions and deposition throughout the document.

A discussion of the intended purpose of the Integrative Synthesis (Chapter 7) and the choice for its location would be useful. From the 15 February 2006 Memorandum from Lester Grant to Fred Butterfield, I presume this is an Integrative Synthesis of health related topics only; if so, this should be stated clearly in the chapter title in the Table of Contents. As it is listed now, the chapter appears to be a synthesis of the entire subject and if that is the case, it is unclear why it occurs before Chapter 8.

Charge Question H1:

Yes the subject section adequately covers the most current and most important information on the measurement methods, distribution and effects of Pb on terrestrial ecosystems. All major bodies of work have been included. There can be better organization of the material, and some inconsistencies can be removed. These minor weaknesses of the document may be the result of a multi-author team, or perhaps they reflect an organizational structure not immediately clear to me. I look forward to discussing this subject at the meeting.

The authors make it abundantly clear that the reduced use of Pb additives in gasoline has decreased substantially the atmospheric deposition of Pb in the US since the mid-1970s. However, information related to the relative role of other sources of Pb is inconsistent in Chapter 8. Page 8-1 line 11 lists waste incineration before the combustion of fossil fuel and metal smelting and production, yet it is not clear if this is listed in order of importance, today or historically, or if the list is random. The same ordering appears on page 8-35 (lines 30-33) and lists the same references (in the opposite order). In this instance, fuel combustion is not included. Certainly, even without gasoline additive Pb emissions, the natural occurrence of Pb in coal and petroleum products other than natural gas should be mentioned. Page 8-47, lines 21-24

include the metal production industry and the combustion of fossil fuels but do not mention waste incineration.

Charge Question H2:

Yes the subject section adequately covers the most current and most important information on the measurement methods, distribution and effects of Pb on aquatic ecosystems.

The following comment is relevant for both H1 and H2: Multiple contaminants, interactions with other pollutants, chemical mixtures including synergistic effects of Pb plus other metals are discussed in multiple locations and in different ways throughout the terrestrial and aquatic ecosystem sections. There are also discussions on this topic elsewhere in the document. This is another area where consistency and uniformity, when appropriate, at least throughout Chapter 8, would be beneficial. The Metal Assessment Panel of the Science Advisory Board of the EPA addressed the issue in its two reports of 2003 and 2005. It might be useful for the thought process from that group on how to address "mixtures" in terrestrial and aquatic ecosystems and in human systems to be communicated to the authors of this document.

The specific case study illustrated in the aquatic section 8.2.6.2 is useful and effective. It would be valuable to discuss if the case study should be expanded and whether or not a parallel treatment of a case study in the terrestrial section would be beneficial.

Charge Question H3:

I believe that the subject section does contain the most current information on the potential use of critical loads. This is a difficult question to answer, and a difficult topic to write about because there are many fewer publications on critical load analysis for metals than there are critical load analysis publications for sulfur, nitrogen and hydrogen ion. Furthermore, the most important document referred to in this section is a paper I was not aware of previously, DeVries et al. (2004), which is not a peer-reviewed document and appears to be available only from a website. Perhaps the panel could discuss the paucity of information on this subject and the apparent lack of any critical loads analysis literature for Pb in the United States, and how to best respond to this relative lack of information. I believe that critical load analysis in general—not even specifically critical load analysis for metals—is relied upon much less in the USA than in Europe and perhaps Canada. Perhaps this too could be a topic for discussion among panelists.

Specific items needing clarification or elaboration:

Page 8-1 lines 19-20. The statement "Pb leached into mineral soil appears to be 20%-50% of total anthropogenic Pb deposition" needs a reference and needs elaboration. At a minimum, it should refer to a specific location or region.

Page 8-18, Figure 8-1.2.1 Relationship of bioaccessibility versus speciation. This figure needs units and needs a better description. Is this an illustration or should the x and y axes confer a scale and directionality?

Page 8-80, Figure 8-1.5.1 Avian toxicity data…. This figure needs units or an indication of directionality on the x axis.

Page 114, lines 4-6. Other studies in this section are described and the percentage reduction that occurred over time is presented. In the discussion of Evans et al. (2005), the percentage reductions are not presented. Why not?

Dr. Robert Goyer

February 24, 2006

From: Robert A. Goyer

To Rogene Henderson, CASAC Chair; Fred Butterfield, CASAC Federal Officer

Comments in response to charge questions E 1

I am not aware of new animal studies not included in the CASAC draft but have some comments regarding sub-questions as follows.

E1a. **Neurotoxicology**

I am not able to provide comments on mechanisms of neurotoxicology, section 5.3.1 but do have comments in regard to organization and continuity for other parts of Section 5.3.

The section (not numbered) beginning on p. 5-66 titled **Dose-response paradigms** serves to connect neurological toxicities to the next chapter, clinical effects, in section 6.3. I suggest this Dose Response discussion is a good bridge to the clinical chapter and might directly follow section 5.3.1. The discussion in **Dose-Response Paradigms** also addresses the **Charge Question E1f** .

The remainder of section 5.3 might be reorganized to provide better emphasis on the toxicological basis for vulnerable populations and susceptibility. Reasons and rationale for reorganizing the remainder of section 5.3 are contained in the following comments.

The third bullet, p. 5-43 **Integration of research findings** questions the rationale for studying susceptibility factors in animals

There are compelling reasons for understanding susceptibility factors. It is true that susceptibility of humans to lead toxicity is difficult to study in experimental models but much has been learned about effects of nutrition, and age on susceptibility from animal studies that has lead to further studies in humans. Factors affecting susceptibility may explain differences in health (toxic) effects that might be observed in different people with comparable levels of exposure and/or biomarkers of exposure and perhaps differences in responses among different age groups. Also, it may be possible to create genetic models in animals that imitate human polymorphisms. To say that there is a “lack of compelling rationale for their investigation” (in laboratory animals) is likely to discourage further research.

Susceptibility factors e.g., nutrition, polymorphisms etc. are well stated in p- 5-51, para. 2 lines 13-23 but are not highlighted as such.

Section 5.3.2 concerns effects of lead in at different ages and the influence of various susceptibility factors. The organization of this Section (5.3.2 p.5-43 line 22 etc) is difficult to follow largely because of dividing the discussion into major groups based on age e.g. 5.3.2.1(p.5-44) Children and adolescents, 5.3.2.2 (p 5-70), Adults with childhood lead poisoning and 5.3.2.3 (p 5-73), Adults with ambient exposures. This organization may be meant to parallel epidemiological studies addressed in Chapter 6. However, many of the subsections in this part of the chapter concern susceptibility factors, e.g. effects of age, nutrition , polymorphisms. This results in repetitions/redundancies in some topics.

The following is a suggested format for reorganization of sections 5.3.2 etc.

Discussion of biomarkers of exposure/effect is fine in introduction.

Susceptibility Factors might be highlighted as a major subsection including Age, SES, Nutrition and polymorphisms (currently two nutrition and polymorphism sections) are under children and adults. This new section might end with a series of conclusions regarding susceptibility factors. It should also reference related discussion of role of other metals on Pb distribution beginning in section 5-7, p. 5-178.

Biochemical biomarker discussion in adult section p5-74, 75 really identifies homocystine as a susceptibility factor and might be considered as such or might even be included as a polymorphism.

P 5-75 para. 2, line 18 begins a section titled, “Vulnerability and Susceptibility” which includes discussion of SES and nutrition, (redundancy). This section might be an introduction to a major section on Susceptibility.

P 5-78, section titled *Neurotoxicology of Lead* is really a discussion of bone lead as a biomarker and might be included with earlier discussion of other biomarkers.

Other sections in 5-3 on neurotoxicology including Neuro Epidemiological studies, p 5-68, Clinical aspects of Adult lead poisoning, p.5-70 appropriately precede the next chapter on epidemiology but are concerned with relationships between experimental studies and clinical indications of lead health effects. These sections currently are not followed by a set of conclusions.

Question E1b. Bone and teeth as internal pools. No comment.

Question E1c. Relevance of study of chelation of lead in animals to humans

Section 5.10.1.4 provides a detailed account of the effects of chelating agents on oxidative stress in the liver. A broader discussion of effects of chelating agents on toxicity in other organ systems, particularly the CNS, would provide information on changes in tissue/cellular content of lead and effects on mechanisms (neural transmitters). Such information provides background for the selection and potential role of chelating agents in management of lead exposure in

humans. The present draft contains very little about experimental studies of effects of chelating agents, only as oxidants (Section 5.2 re: as erythrocyte antioxidants, also section 5.10.1.4 Effects of Chelation on ROS p 5-p266).

Question E1d. Do insights gained on Pb-induced alterations in erythrocyte biology do provide information regarding molecular mechanisms of action? Yes.

Section 5-1 reviews effects of lead on erythrocyte biology and function, heme metabolism and erythrocyte enzymes. The section is clearly written and provides a detailed summary of current information of lead in the red blood cell**.** Many of the heme intermediates and enzymes are used as biomarkers for assessment of both lead exposure and potential health effects so mechanisms of action of lead on these molecular systems is important in understanding the significance of changes in red blood cell metabolism. As to whether they are suggestive of mechanisms underlying specific health points I believe the answer is yes. For example, interactions of Pb and Ca on membrane transport are likely to be similar to effects on transport in kidney tubule cells, hepatic cells and possibly cells in the CNS.

Question E1e. Is the oxidative stress theory plausible for Pb toxicity?

The answer is yes

Oxidative stress is likely as a common mode of action operating across organs and species. It is cited and discussed as a mode of action in various organ systems in this chapter. Oxidative stress has been invoke and a common mode of action for toxicity of other metals as well as Pb so that it is non specific and other more specific modes of action must be present in different organ systems to explain differences in effects between organs and between different metals.. It is likely a common mode of action but is non-specific and not the only mode of action. Role of oxidative stress is discussed in section 5.2.6 including effects of antioxidants on reducing B-Pb levels.

Question E1f. How to use animal data to identify cut-off values for lead effects in humans?

It is difficult directly extrapolate quantitative data from animal studies to humans but results in animals can suggest that there may not be a cut-off value for a particular effect in humans, e.g Pb induced increases in NMDA receptor density, p5-23 line 7-9, and may indicate beneficial or adverse effects of modifying factors, e.g. nutritional supplements, dose-response, PB/Ca).

The discussion of **Integration of Research Findings** (neuro)at the end of section 5.3.1 and bullet 2 on page 5-43 debates low level effects of lead on the CNS in animal models. From my own experiences many years ago it was clear that it required a much higher blood lead level in the rat to attain a particular brain lead level than in a human so there are clearly species differences. However, animal models might address the question of reversibility. Also animal models might address the question of linearity of effect at low levels of exposure

Other examples that show how animal studies assist in identifying low-level sub-clinical effects are cited in section 5.4, e.g. (p 5-93 para 1). Placental effects of Pb exposure in squirrel monkeys

were determined without overt toxicity to mothers, page 5-94 para 5.4.3.4. Pb induced endocrine mediated alterations of female reproductive system of rats and non-human primates suggest that non-human primates are particularly relevant to extrapolations to humans and provide dose-response information for effects on female sex hormones and menstrual cycle.

Other comments about specific sections in Chapter 5

Section 5.2 Effects on Heme Synthesis

Section is well written, succinct with good summary. Last three paragraphs of section 5.2 concerns chelation as protective antioxidants for erythrocytes. Para 2 page 5-16 second sentence makes the general statement that metal chelators form **insoluble** complexes. Shouldn't that be **soluble** complexes?

Summary for this section 5.2.7 is very good.

Section 5.3 Neurological Effects

See comments in response to Charge question E1.

Section 5.4 Reproductive Effects

Section 5.4.7.3 **(p5-104) Developmental effects on the** Retina might be crossed referenced with Section p 5-31 **Retinal function in Rodents** (not numbered**).**

Conclusions to this section p 5104-108 are really a lengthy repletion with cited references of earlier text. Might be integrated into the chapter followed by a more succinct set of conclusions.

Section 5.5 Effects on CV system.

No comments, Good summary and conclusions p5130-131.

Section 5.6 Genotoxic and Carcinogenic Effects

Section 5.6 P5-135 lines 1-3 the statement that the "data (from the Waalkes et paper on MT-null mice) convincingly indicate that metallothionein binds Pb as part of an inclusion body and prevents tumors" is not correct. Pb induced inclusion bodies are not formed in mt-null mice. The study is correctly interpreted page 5-293, line 28-29, – that mt (gene) or a closely related gene is involved in the formation of Pb-binding proteins in the kidney.

Section 5.6.6 Conclusions. I agree that overall conclusions have not changed much since the 1986 Pb AQCD.

Section 5.7 Lead and the Kidney

This section is well done. I suggest adding in summary Section 5.7.5 that earlier experimental studies have shown that acute effects on tubular cells are generally reversible. With continued exposure acute renal effects may progress to a chronic irreversible nephropathy. Also none of the biomarkers for renal effects are specific for lead effects on the kidney.

I have no comments on Section 5.8 Effects on Bone and Teeth and Section 5.9, Effects on Immune system

Section 5.10 Other organ systems

Series of heterogeneous topics.

Summary 5.10. 1(re: liver effects) is v. good.

Summary of Section on Gasrointestinal absorption 5.10.2.7 is good and summarizes factors that influenced rate/percent of absorption. However, I did not find any discussion of this in this document particularly concerns about effects of chemical speciation of lead absorption, e.g Pb acetate versus Pb sulfate and exposure to dust, lead ores, mine tailings etc. Is all of this incorporated in the modeling Chapter.?

Section 5.11 Lead-binding proteins is a complex topic which is still evolving.

Separating the discussion of proteins in the intranuclear inclusion body from cytoplasmic lead binding proteins implies that the proteins involved may be different. That may not be the case. The paper describing the formation of inclusion bodies by Mclaughlin et al. 1980 (cited in another context line 29, p284, describes the ultrastructural appearance of fibrils in the cytoplasma in response to lead exposure with subsequent formation of intranuclear inclusion bodies. These studies suggest that intranuclear inclusion body protein may be derived from the cytoplasm. I suggest that sections 5.11.1 and 5.11.2 be merged with inclusion of the McLauglin et al.1980 observation .

Also discussion of the studies by Harry, et al. 1996 (Tox Appl Pharmacol 139:84-93) regarding fibrillar acidic protein in the developing rat brain should also be included. This fibrillary protein has some similarities to inclusion body protein described by Goyer et al. 1970a and Moore and Goyer, 1974.

Lead binding protein in erythrocytes seems to be an independent phenomenon but inconclusive at this point. The proteins describe by Fullmer et al. (1985) in the intestine are more likely Ca transport proteins as suggested.

The summary or a newly written conclusion section might provide a synthesis of the different studies and approaches to metal binding proteins and how they are similar/different.

The summary does not include a comment about inclusion body protein.

Discussion of Mt in bullets in the second and fourth bullet might be combined.

March 10, 2006

From: Robert A. Goyer

To Rogene Henderson, CASAC Chair; Fred Butterfield, CASAC Federal Officer

Post-meeting review comments on 1st draft Pb AQCD

I was not in attendance when Chapter 5 was discussed but would like to submit the following brief comments based on my earlier review and the review meeting discussions I did attend.

Chapter 5 needs to be better organized to provide balanced treatment of the topics in each. Also redundancies should be omitted and there should be succinct conclusions at the end of each section. The 1st draft is into 11 sections concerning 10 organ systems and one section, and a last one, on lead- binding proteins. I suggest consolidating discussions regarding various susceptibility factors into a new single section including the following topics.

Polymorphisms/genetics

Nutrition

Age, all ages? (from conception to the elderly)

SES

Biochemical biomarker discussion in adult section p5-74, 75 really identifies homocystine as a susceptibility factor and might be considered as such or might even be included as a polymorphism.

There might also be some discussion concerning role of other metals on Pb distribution beginning in section 5-7, p. 5-178.

The section (not numbered) beginning on p. 5-66 titled **Dose-response paradigms** serves to connect neurological toxicities to the next chapter, clinical effects, in section 6.3. I suggest this Dose Response discussion is a good bridge to the clinical chapter. This might form part of a succinct summary of the whole chapter.

The following comments were included in my pre review meeting submission but concern corrections and omissions I wish to emphasize

Section 5.2 Effects on Heme Synthesis

Section is well written, succinct with good summary. Last three paragraphs of section 5.2 concerns chelation as protective antioxidants for erythrocytes. Para 2 page 5-16 second sentence makes the general statement that metal chelators form **insoluble** complexes. Shouldn't that be **soluble** complexes?

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Also discussion of the studies by Harry, et al. 1996 (Tox Appl Pharmacol 139:84-93) regarding fibrillar acidic protein in the developing rat brain should also be included. This fibrillary protein has some similarities to inclusion body protein described by Goyer et al. 1970a and Moore and Goyer, 1974.

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The summary or a newly written conclusion section might provide a synthesis of the different studies and approaches to metal binding proteins and how they are similar/different.

The summary does not include a comment about inclusion body protein.

Discussion of Mt in bullets in the second and fourth bullet might be combined.

Mr. Sean Hays

Comments on Chapter 4 – Lead NAAQS

Submitted by: Sean Hays (Summit Toxicology)

Chapter 4 includes descriptions of most of the major lead kinetic models available for relating environmental and dietary lead exposures with blood lead in humans. Chapter 4 includes a description of the All Ages Lead Model (AALM), which is probably inappropriate given its' incomplete status. It should be included once it has been formally accepted by the All Ages Lead Model review panel of the Science Advisory Board.

The glaring omission from Chapter 4, and is contained no where else in the rest of the lead NAAQS document, is a description of the pharmacokinetics of lead in humans. While the models described in Chapter 4 synthesize what is known about the pharmacokinetics of lead, a knowledge of the underlying pharmacokinetic science is required for reviewers to understand and appreciate, 1) how historical exposures to lead can impact current blood lead levels, 2) how pharmacokinetics of lead in particular populations yield some sensitivities, and 3) how transient changes in exposure may or may not be an important contributor to blood lead levels and thus impacts on public health. Therefore, Chapter 4 should include a review of the pharmacokinetics of lead in humans, with particular emphasis placed on sensitive populations, including;

- In utero exposures
- Children, including neonates,
- Potential for lead to be excreted in breast milk
- Post-menopausal women and individuals with osteoporosis

It is not enough to simply review the models of lead pharmacokinetics without a description of the underlying pharmacokinetic literature that forms the basis of these models. Given that not all models are applicable for all the sensitive populations, a knowledge of the pharmacokinetics in these populations will be critical for reviewers to understand how the pharmacokinetics of lead in these populations may impact the risk assessment.

Without knowing how a model will be used in developing an air quality standard, it is impossible yet to provide insights on which model(s) would be most appropriate for this exercise. Having an actual requirement and use for a model imposes certain constraints and requirements. Once these are known, more insights can be provided on which model(s) are valid and/or best suited for the application, in this case for a risk assessment of lead.

The following are specific comments on Chapter 4.

Page	Line	Comment
4-10	29	The term “probabilistic model” is inappropriate as a description of the IEUBK model
4-13	1	“unlimited” should be replaced with the term “linear”
4-13	6	replace “a function of” with “with increasing total lead intake and age”
4-13	7	Need to define what is meant by absorption fractions are medium specific.
4-13	17	The reference to Table 4-1 seems to indicate different content than actually exists.
4-17	25	Reference to “probability of elevated” should be deleted. The model is actually designed to predict blood lead concentrations, not probability of elevated blood lead levels.
4-18	7	It is not accurate to describe the GSD function as a “probability model”
4-26	9	The PBPK model has been used to address post-menopause and osteoporosis (O’Flaherty, 2000). This should be included here and in various other places later in the chapter.
4-26	23	The reference to 70% and 30% are backwards. 70% of lead elimination is attributed to urine in the PBPK model.
4-29	14	Another approach is to use a GSD approach like that used in the IEUBK model.

Dr. Bruce Lanphear

Comments on "Routes of Human Exposure to Lead and Observed Environmental Concentrations" (Chapter 3)

General Comments:

The Chapter on "Routes of Human Exposure to Lead" is a good beginning. There are, however, several modifications that would enhance the Chapter. An overview and introduction of the Chapter would be useful. As written, the chapter meanders through various sources of exposure without a logical format or outline. It would also be helpful if the authors provided a description of the scope of the review and the systematic approach that was used to identify the various papers on lead exposure published since 1990. There were major gaps in their literature review and it wasn't clear why there wasn't a greater focus on data to quantify the relative contributions of various sources of lead exposure. If the contribution of various sources of lead exposure is to be included in the Synthesis Chapter, it would be worth noting this in the introduction.

This overview should include insights that would help the reader understand the contribution and trends in lead exposure. For example, it may not be obvious to all readers that the various sources of lead intake are cumulative, and that blood lead (in children) and bone lead (in adolescents and adults) are cumulative biomarkers of exposure.

Charge Question C1. Does Chapter 3 provide adequate coverage of pertinent available information (especially as it pertains to the United States) on lead exposure routes, as well as environmental lead concentrations, including those in air, drinking water, food, soils, and dust? Does the chapter adequately delineate interconnections between airborne lead and its potential contributions (via secondary deposition) to lead in other media (e.g. indoor dust)?

As written, the Chapter does not delineate the interconnections between airborne lead and other media. Nor does it adequately cover the available information on routes of lead exposure. Most of the following specific comments attempt to fill some of those gaps. The description of the contribution of airborne lead was inadequate.

Given that dust is the most proximal exposure for contemporary children, it deserves considerably more attention. There is now considerable data on the probability of a child having a blood lead level > 10 μg/dL if exposed to various levels of lead-contaminated house dust. In 2001, the US EPA promulgated residential lead standards of 40 $\mu g/ft^2$ for floors and 250 $\mu g/ft^2$ for window sills. Data from epidemiologic studies show that 5% of children have a blood lead level ≥ 10 μg/dL at a median floor dust lead level of 5 $\mu g/ft^2$ (Lanphear, 1996; Lanphear, 1998; Malcoe, 2002; Lanphear, 2005). At a floor standard of 50 $\mu g/ft^2$, 20% of children were estimated to have a blood lead level ≥ 10 μg/dL (Lanphear, 1998). Children who were exposed to floor dust lead levels ≥ 25 $\mu g/ft^2$ were at 8-times greater risk of having blood lead levels ≥ 10 μg/dL compared with those exposed to levels below 2.5 $\mu g/ft^2$ (Lanphear 2005).

Malcoe LH, Lynch RA, Keger MC, Skaggs VJ. Lead sources, behaviors, and socioeconomic factors in relation to blood lead of native american and white children: a community-based assessment of a former mining area. Environ Health Perspect. 2002 Apr;110 Suppl 2:221-31.

Lanphear BP, Hornung R, Ho M. Screening housing to prevent lead toxicity in children. Pub Health Rep 2005;120:305-310.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. J Pediatr. 2002 Jan;140(1):40-7.

Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.

As to the contribution of airborne lead to interior house dust, there is an article by Caravanos and others that should be incorporated even though it was only published in 1996. Caravanos collected weekly sample collection of interior and exterior settled dust in New York City to monitor accumulation of atmospheric deposition of lead (Caravanos, 2006). The median values of leaded dust for the interior plate (adjacent to the open window), unsheltered exterior plate, and the sheltered exterior plate were 4.8, 14.2, and 32.3 $\mu g/feet^2/week$, respectively. The data suggest that there is a continuous source of deposited leaded dust in interior and exterior locations within New York City. Additional data from a control plate (interior plate with the window closed) showed that the source of the interior lead deposition was primarily from exterior (environmental) sources.

Caravanos J, Weiss AL, Jaeger RJ. An exterior and interior leaded dust deposition survey in New York City: Results of a 2-year study. Environ Res. 2006;100:159-164.

Introduction (or embedded in the section on various sources of lead exposure):
It would be useful if the authors would provide a description of the relative contribution of various sources of lead exposure that vary by age. Children's blood lead levels rise rapidly between 6 and 12 months of age, peak between 18 months to 36 months and then gradually decline (Clark, 1991). The peak in children's blood lead levels is due to the confluence of normal mouthing behaviors and increasing mobility. Lead-contaminated floor dust is a source of lead intake throughout early childhood, but lead-contaminated dust on windowsills is not a major source of intake until the second year of life, when children stand upright. Soil ingestion, as reported by parents, peaks during the second year of life and diminishes thereafter (Lanphear, 2002).

Clark S, Bornschein R, Succop P, Roda S, Peace B. Urban lead exposures of children in Cincinnati, Ohio. Chemical Speciation Bioavailability 1991;3:163-171.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. J Pediatr. 2002 Jan;140(1):40-7.

It would also be useful if the authors could summarize how our understanding of lead exposure has changed since the 1990 supplement. For example, there have been several randomized trials published since 1990 that provide insight into the relative contribution of lead intake from various sources that were entirely overlooked by the authors. In a meta-analysis of 4 dust control trials and 1 low-cost housing intervention, there was no significant reduction in children's mean blood lead concentration (Haynes, 2001). There was, however, a > 50% reduction in children having blood lead concentrations ≥ 15 μg/dL and ≥ 20 μg/dL in the experimental groups compared with the control groups, indicating some benefit of dust control for children with higher blood lead levels (Haynes, 2001). Since the publication of this systematic review, two additional studies were published (Jordan, 2004; Brown, 2005). One community based study showed a 34% (non-significant) reduction in the proportion of children with a blood lead level ≥ 10μg/dL (Jordan, 2004). As described later, there have been studies of soil abatement that provide insight into the contribution of lead from soil (e.g., Aschengrau, 1994).

Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of dust controls on children's blood lead concentrations: A systematic review. Env Health Perspect 2001;110:103-107.

Jordan CM, et al. A randomized trial of education to prevent lead burden in children at high risk for lead exposure: efficacy as measured by blood lead monitoring. Environ Health Perspect. 2003;111:1947-51.

Aschengrau A, Beiser A, Bellinger D, Copenhafer D, Weitzman M. The impact of soil lead abatement on urban children's blood lead levels: phase II results from the Boston Lead-In-Soil Demonstration Project. Environ Res 1994;67:125-148.

Brown MJ, McLaine P, Dixon S, Simon P. A randomized, community-based trial of home visiting to reduce blood lead levels in children. Pediatrics. 2006 Jan;117(1):147-53.

Page 3-1, line 12-21: This paragraph leaves the impression that exterior sources of lead are more important source of lead in house dust than interior sources, such as lead-contaminated paint. This may be true for mining, milling or smelting communities, but it is not true for many older urban communities. (I am certainly not trying to revive or perpetuate the old "environment versus housing" wars; my interpretation is that they are probably contributing equally and both certainly need to be reduced to impact human exposure.) The statement also needs to be clarified because there is evidence that paint is a particularly important source for children with *elevated* blood lead levels (Sachs 1970; McElvaine, 1990; Shannon 1995; Bates, 1995; Lanphear 1996).

There are several relevant studies shed some light on this specific question about sources of lead in house dust. Hunt used a classification scheme to categorize the house dust particles as auto exhaust, road dust, garden soil or paint in England (Hunt, 1993). The primary contributing source in the 64-1000-microm size range of the house dusts was paint. In the 0-64-microm size fraction, paint, road dust and garden soil all made significant contributions.

In a U.S. study, Sterling and others showed that all three sources – mining waster, paint and soil – were determinants of house-dust. Not surprisingly, they concluded that soil and mining wastes accounted for over 50% of lead in house dust whereas only 16% (23% using a weighted formula to account for the lead concentration per particle) was from paint (Sterling, 1998). Paint was responsible for 16% to 23% (29% was of unidentified origin) of lead in house dust in a mining community (Sterling, 1998).

Adagte et al. used lead stable isotope ratio analysis examine the relationship between sources of lead in 22 dust wipe samples collected from 10 homes in Jersey City, NJ (Adgate, 1998). They found high correlations between isotope ratios of wipe samples for street dusts and exterior soils, indicating that these two sources were indistinguishable. They were treated as a single exterior source in a source apportionment using isotope ratio matching. The upper-bound estimate of the contribution of interior lead-based paints to 10 floor- and eight sill-wipe samples was 56% and 50%, respectively (Adgate, 1998).

In a case study of two households in Oakland, California, Yaffe et al. found that paint and surface soil samples collected in and around both households of children with elevated blood lead levels (Yaffe, 1983). The isotopic ratios of lead in the blood of these children were close to the average lead ratios of paints from exterior walls and of surface soils in adjacent areas where the children played. In both case studies, the data suggest that the lead in the soil was derived mainly from weathering of lead-based exterior paints and that the lead-contaminated soil was a proximate source of lead in the blood of the children.

In a study from New Zealand, Bates and coworkers found that children with elevated lead levels were more likely to live in a house greater than 50 years old where paint removal had taken place in the last 2 years (RR = 14.4, 95% CI: 2-107) (Bates, 1995). Eating dirt, particularly for children who usually played outside within 2 meters of the house, was also a risk factor for elevated blood lead levels. Soil lead levels increased with the age of the house and were correlated with blood lead levels ($r = 0.32$).

In a study to examine risk factors to explain the racial differences in children's blood lead concentrations, the primary differences in exposure that explained racial disparities in children's blood lead concentration were dust lead loading and paint lead variables (Lanphear, 1996). Predictors of blood lead concentration for Black children, who had a geometric mean blood lead of 8.8 μg/dL, were dust lead loading, paint lead concentration and condition, water lead, soil lead concentration and putting soil or dirt in their mouths. In contrast, predictors for White children, who had a geometric mean blood lead of 4.4 μg/dL, was limited to soil lead concentration, time spent outdoors, and putting soil or dirt in their mouths (Lanphear, 1996). The authors concluded that a major reason for the racial disparity (and the significantly higher blood lead levels) was that Black children were exposed to *both* interior and exterior sources of lead.

Page 3-2, line 22-31: The authors should consider discussing other relevant research using isotopic ratios to enhance the discussion of the source of lead in housing (see Gwiazda RH, et al. EHP 2000;108:1091-1097).

It is also worth noting that airborne lead and exterior lead may be derived from lead-based paint due to demolition or remodeling of other dwellings (Farfel, 2003).

Sterling DA, Johnson DL, Murgueytio AM, Evans RG. Source contribution of lead in house dust from a lead mining waste superfund site. J Expo Anal Environ Epidemiol. 1998 Jul-Sep;8(3):359-73.

Hunt A, Johnson DL, Thornton I, Watt JM. Apportioning the sources of lead in house dusts in the London borough of Richmond, England. Sci Total Environ. 1993 Sep 30;138(1-3):183-206.

Adgate JL, Rhoads GG, Lioy PJ.The use of isotope ratios to apportion sources of lead in Jersey City, NJ, house dust wipe samples. Sci Total Environ. 1998 Oct 8;221(2-3):171-80.

Yaffe Y, Flessel CP, Wesolowski JJ, del Rosario A, Guirguis GN, Matias V, Gramlich JW, Kelly WR, Degarmo TE, Coleman GC. Identification of lead sources in California children using the stable isotope ratio technique. Archives of Environmental Health 1983;237-45.

Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: report of 1,155 cases. Pediatrics 1970;46:389-396.

McElvaine MD, DeUngria EG, Matte TD, Copley CG, Binder S. Prevalence of radiographic evidence of paint chip ingestion among children with moderate to severe lead poisoning, St Louis, Missouri, 1989 through 1990. Pediatrics 1992;89:740-742.

Shannon MW, Graef JW. Lead intoxication in infancy. Pediatrics 1992;89:87-90.
Bates M, Malcolm M, Wyatt R, Garrett, N, Galloway Y, Speir T, Read, D. Lead in children from older housing areas in the Wellington region. New Zealand Medical Journal 1995;108:400-404.

Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.

Farfel MR, Orlova AO, Lees PS, Rohde C, Ashley PJ, Chisolm JJ Jr.A study of urban housing demolitions as sources of lead in ambient dust: demolition practices and exterior dust fall. Environ Health Perspect. 2003;111:1228-34.

Page 3-1, line 27: There are several other relevant articles that should be cited to indicate that various methods of lead hazards control can result in an increase in children's blood lead levels, especially for young children who exhibit frequent mouthing behaviors. (Amitai, 1991, Rey-Alvarez 1987, Swindell 1994, Aschengrau 1997, Clark 2004).

Two studies of paint abatement are particularly noteworthy because they show that undue lead exposure can occur despite the use of dust clearance tests after lead abatement (Aschengrau, 1997, Clark 2004). In a prospective, controlled study of children with baseline blood lead below 22 µg/dL, Aschengrau reported a 6.5 µg/dL increase in blood lead for children who had paint abatement (Aschengrau, 1997). Clark and coworkers found, despite using HUD post-abatement

standards, that 6-month old children were 11-fold more likely to have an increase in blood lead concentration > 5 μg/dL. Collectively, these studies raise questions about the adequacy of existing clearance standards to protect children from lead hazards following abatement or other lead hazard controls, especially for younger children (Clark, 2004).

Amitai Y, Brown MJ, Graef JW, Cosgrove E. Residential deleading: effects on the blood lead levels of lead-poisoned children. Pediatrics 1991;88:893-8987.

Rey-Alvarez S, Menke-Hargrave T. Deleading dilemma: Pitfall in the management of childhood lead poisoning. Pediatrics 1987;79:214-217.

Swindell SL, Charney E, Brown MJ, Delaney J. Home abatement and blood lead changes in children with class III lead poisoning. Clin Pediatr 1994;33:536-541.

Aschengrau A, Beiser A, Bellinger D, Copenhafer D, Weitzman M. Residential lead-based-paint hazard remediation and soil lead abatement: their impact among children with mildly elevated blood lead levels. Am J Public Health 1997;87:1698-1702.

Clark S, Grote J, Wilson J, Succop P, Chen M, Galke W, McLaine P. Occurrence and determinants of increases in blood lead levels in children shortly after lead hazard control activities. Environ Res. 2004:(2):196-205.

Page 3-2, line 7: The authors usually refer to dust lead concentration, but some of the studies express dust in loading ($\mu g/ft^2$). This raises the question about whether concentration or loading is a better measure of exposure. While there are some advantages to dust lead concentration (mostly limited to modeling), dust lead loading is a significantly better predictor of children's blood lead levels (Lanphear, 1995; Lanphear 1998). Indeed, the US EPA residential dust lead standards rely on dust lead loading, not concentration. This distinction is key to understand childhood lead exposure.

Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.

Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.

Page 3-4, Table 3-1: The description and tabulation of dust lead levels is vague. I would imagine, for example, that the reason Cincinnati had dust lead loading values ranging from 20 $\mu g/ft^2$ to 293 $\mu g/ft^2$ is because they were collected from various surfaces. But the reader is left to guess why the levels vary. This raises the problem of treating all dust lead levels the same regardless of whether they were collected from different surfaces using different sampling methods (e.g., floor versus window sill or window trough).

Page 3-1, lines 6-29:
The authors indicate that soil is an important source of lead exposure, but their review did not include more recent studies that attempted to estimate the contribution of lead to children's lead intake. Duggan and Inskip estimated that children's blood lead concentrations increased 5 μg/dL for every 1000 ppm increase in soil lead concentration, but this estimate didn't account for other sources of lead intake (Duggan, 1985). In a randomized, controlled trial of soil abatement, Aschengrau and coworkers reported a 1.12 to 1.35 μg/dL decrease in blood lead for every 1000 ppm reduction in soil lead concentration (Aschengrau, 1994). In a pooled analysis of 12 studies, there was an estimated 3.8 μg/dL increase in blood lead concentration for every 1000 ppm increase in soil lead concentration (Lanphear, 1998). Finally, in a Superfund site, soil abatement was shown to lead to a 3.5 μg/dL decrease in blood lead levels of 6 to 36 month old children; the decrease was less for 36 to 72 month old children (Lanphear 2003). The variation in the reported relationship of lead-contaminated soil is due to a number of factors, including the age of children studied, adjustment for the contribution of lead intake from other sources, and mouthing behaviors. Indeed, once adjusted for age (i.e., redistribution of bone lead stores – see Gwiazda R, Campbell C, Smith D. A noninvasive isotopic approach to estimate the bone lead contribution to blood in children: implications for assessing the efficacy of lead abatement. Environ Health Perspect. 2005;113:104-10) the estimated contribution of soil lead to children's blood lead concentration from these latter three studies is quite similar.

Duggan MJ, Inskip MJ. Childhood exposure to lead in surface dust and soil: a community health problem. Public Health Rev 1985;13:1-54.

Aschengrau A, Beiser A, Bellinger D, Copenhafer D, Weitzman M. The impact of soil lead abatement on urban children's blood lead levels: phase II results from the Boston Lead-In-Soil Demonstration Project. Environ Res 1994;67:125-148.

Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.

Lanphear BP, Succop P, Roda S, Henningsen G. The Effect of Soil Abatement on Blood Lead Levels in Children living near a Former Smelting and Milling Operation. Public Health Reports 2003;118:83-90.

Page 3-9, lines 1-6: It would be helpful if there was additional and more specific information about the four areas (Liberty-Acadia, MO, Herculaneum MO, East Helena, Lame Deer, MT) that exceeded the EPA air lead standard, including trends over the past 5 to 10 years because these sites are likely to be of particular interest and relevance to the review. Although the authors write that only two sites exceeded EPA standards in 2004, my understanding is that Herculaneum (MO) once again exceeded standards again in 2005. Was this one of the sites? It would useful to plot the airborne levels of lead for each of the sites up to the present.

Page 3-11: The authors describe occupational exposure, but they do not consider or describe para-occupational (take-home) exposures for children (see Roscoe, 1999). This includes construction, lead mining and smelting, renovation or construction workers, and manufacturing. There can also be community exposure from paint removal of bridges.

Roscoe, RJ, et al. Blood lead levels among children of lead-exposed workers: A meta-analysis. Am J Ind Med 1999;36:475-481.

Page 3-13, line 1-10: If the authors want to conclude that "The dominant source of lead to soil is atmospheric deposition from local sources and long-range transport." they either need to put some conditions on this statement to indicate a specific setting or more thoroughly review the literature to make a convincing argument.

Page 3-14, lines 16: All of the studies the authors cite to argue that "the major source of lead in the urban environment is soil" did not measure paint lead. Thus, it is not a surprise that age of housing or paint wasn't found to be a major contributor to lead in soil. (To be fair, most of the urban studies did not examine the contribution from airborne lead. Still, the authors should be careful not to over-interpret the conclusions of studies that did not evaluate all sources of lead exposure.) In one study, for example, which studied housing units in an urban setting, paint lead concentration and deteriorated lead-based paint predicted soil lead concentration (Lanphear 1998). Jacobs reported that soil lead levels were related to deteriorated exterior lead-based paint. They found that for units with and without deteriorated exterior lead-based paint, the percent of units with bare soil lead levels ≥ 1,200 ppm decreased from 24% to only 4% (Jacobs, 2002). Thus, as written, the statement that "the major source of lead in the urban environment is soil" is overly broad.

Jacobs DE, et al. The Prevalence of Lead-Based Paint Hazards in U.S. Housing. Environ Health Perspect 110:A599–A606 (2002).

Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. Environmental Research 1997;74:67-73.

Page 3-33, lines 8-18: I found it odd that lead-based paint was mentioned almost as an afterthought when it is arguably the major source of lead exposure for contemporary children, especially those whose blood lead concentrations exceed 10 μg/dL. For a comprehensive review of lead exposure, it would be worth describing that paint that was used through the 1950s, and continuing to some extent through the 1970s, often contained high concentrations of lead. It would also be worth providing insight into the relative contribution from lead-based paint for children with varying degrees of lead exposure. For example, over 80% of children with blood lead levels greater than 50 μg/dL were reported to ingest paint chips or broken plaster (Sachs, 1970). Children with blood lead above 55 μg/dL were 10-times more likely to have paint chips observable on abdominal radiographs than children who had blood lead levels below this value (McElvaine, 1992). The majority of preschool children with blood lead over 25 μg/dL were reported to put paint chips in their mouth (Shannon, 1997). Because all of these children were exposed to background levels of leaded gasoline, these studies really indicate that it was children with exposure to both leaded gasoline and leaded paint that ultimately developed lead poisoning

or elevated blood lead concentrations. Still, this perspective provides insight into past sources and provides an opportunity for the authors to describe trends in childhood lead exposure.

Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: report of 1,155 cases. Pediatrics 1970;46:389-396.

McElvaine MD, DeUngria EG, Matte TD, Copley CG, Binder S. Prevalence of radiographic evidence of paint chip ingestion among children with moderate to severe lead poisoning, St Louis, Missouri, 1989 through 1990. Pediatrics 1992;89:740-742.

Shannon MW, Graef JW. Lead intoxication in infancy. Pediatrics 1992;89:87-90.

Page 3-35, lines: 1-22: There was no mention of soil sampling or dust sampling in the section on measurement methods. Yet, it is well known that dust lead loading varies considerably by the surface sampled and the sampling methods used (Lanphear, 1995). This section should include discussion of how sampling different areas of the floor or using different sampling methods also affects dust lead loading values (Lanphear, 1995). Dust lead loading collected from troughs is oftentimes 1000-fold greater than floors samples. The levels of lead in house dust collected from the midpoint of a room tends to be lower than those found under a window or in the perimeter of a room (Sayre, 1974). Finally, soil lead concentration can vary by location (perimeter of foundation versus yard samples), by the sieve size used, and the depth of collection.

Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.

Sayre JW, Katzel MD. Household surface lead dust: its accumulation in vacant homes. Environ Health Perspect. 1979;29:179-82.

Page 3-35, lines 26-29: In the summary (and on page 3-14, lines 14-16), the authors refer to the fact that "people in cities, especially in poor and minority-dominated neighborhoods, are the most at risk for lead exposure". But, they do not adequately review the literature to clarify the specific differences in the types of exposure by urban status. Similarly, I was surprised that there was no mention of the striking racial disparity in blood lead levels (Pirkle, 1998) due, in large part, to differences in environmental exposures (Lanphear, 2002). This deserves to be included in the review.

Pirkle JL, Kaufmann RB, Brody DJ, Hickman T, Gunter EW, Paschal DC. Exposure of the U.S. population to lead, 1991-1994. Environ Health Perspect 1998;11:745-50.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. J Pediatr. 2002 Jan;140(1):40-7.

In their review of the human exposure to lead-contaminated water, it would be valuable to review evidence on its contribution to blood lead concentrations in pregnant women and children (Watt, 1996), and the trends in its relative contribution to lead intake (Levin 1989). In a

prospective study of 248 children followed from 6 to 24 months, children who were exposed to water lead > 5 ppb had blood lead concentrations 1.0 μg/dL (20%) higher than children with water lead levels < 5 ppb (Lanphear 2002). Thus, water is not a trivial source of lead intake for young children in many communities. Moreover, as predicted, lead in water is becoming an increasingly important source of lead intake as other sources of lead intake have diminished (Levin, 1989).

Watt GCM, Britton A, Gilmour WH, et al. Is lead in tap water still a public health problem? An observational study in Glasgow. BMJ 1996;313:979-981.

Levin R, Schock MR, Marcus A. Exposure to Lead in US Drinking Water. Trace Substances Environ Health 1989;319-344.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. J Pediatr 2002;140(1):40-7.

Page 3-27, lines 26-29: In the section on exposure via food ingestion, it would be important to describe various factors that modify lead absorption. In the experimental setting, for example, fasting has been shown to modify lead absorption in adults. There was a 10-fold increase in lead absorption among fasting volunteers who ingested lead compared with those who had recently eaten (Rabinowitz 1980; Maddaloni 1998).

Maddaloni M, Lolacono N, Manton W, Blum C, Drexler J, Graziano J. Bioavailability of soilborne lead in adults, by stable isotope dilution. Environ Health Perspect 1998;106:Suppl:1589-1594.

Rabinowitz MB, Kopple JD, Wetherill GW. Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am J Clin Nutr 1980;33:1784-1788.

Comments on "Epidemiologic Studies of Human Health Effects Associated with Lead Exposure" (Chapter 6)

QF1. Are the discussions on the various biomarkers adequate to elucidate their role in assessing human health effects from lead exposure?

Yes.

QF1. Does Chapter 6 adequately address the issue of which exposure metrics (i.e., peak, average lifetime or concurrent) are now believed to be most strongly associated with specific health endpoints and, therefore, should be the focus of exposure and risk assessments targeting those endpoints?

Yes, at least for the IQ-blood lead relationship. There is less data on various blood lead or bone lead indices for predicting other outcomes, such as behavior.

QF2a. New human epidemiologic studies provide evidence for IQ decrements associated with blood lead levels <10 μg/dL. The pooled analysis shows a significant inverse relationship of lead concentration and IQ measured at school age, after adjusting for common confounders. Due to the log-linear relationship, the slope of the lead effect on IQ was greatest at the lower blood lead level range, i.e., below 10 μg/dL. Does this chapter adequately address questions regarding significant neurotoxic effects observed at low blood lead levels (<10 μg/dL)?

The Chapter could describe one other aspect of the pooled analysis that is directly related to potential limitations (Lanphear, 2005). There was some criticism that a certain site was driving the results and that the HOME Score was not measured concurrent with the IQ test (Ernhart, 2006). This commentator also pointed out limitations of other sites (e.g., early blood lead tests measured with capillary finger stick rather than venipuncture and inclusion of two geographically distinct villages with disparate levels of childhood lead exposure). In the pooled analysis, we conducted sensitivity analyses to test whether excluding any one of the sites altered the results of the pooled analysis. The analyses showed quite convincingly that no single study was responsible for the estimated relationship of lead and IQ decrements. This finding diminishes the concerns about unique attributes or potential limitations for any specific sites.

Ernhart CB. Effects of lead on IQ in children. Environ Health Perspect 2006;114:A85-6; author reply A86-7.

QF2a. Is the issue of the influence of model selection on the estimated health effects adequately discussed?

No. The pooled analysis used a log-linear analysis to quantify the lead-associated IQ decrements. But it was not explicit in the review that the non-linear relationship observed in the pooled analysis was not due to the influence of the log-linear model. The following points would help to clarify this:

1. Using a cubic spline regression analysis, which doesn't assume any particular shape of the relationship, the lead-associated IQ decrements were greater at lower blood lead levels.

2. The log-linear analysis agreed remarkably well with the cubic spline analysis compared with other models.

3. Using linear models for blood lead levels above and below 7.5 μg/dL, the slope was significantly steeper at lower blood lead levels compared with the slope at higher blood lead levels.

4. The log-linear model will tend to exaggerate the slope at the lowest blood lead levels; as a result, the authors provided estimates for the lead-associated IQ decrements from < 1 μg/dL to 10 μg/dL as well as from 2.4 μg/dL to 30 μg/dL (representing the 5^{th} to 95^{th} percentile) (Lanphear, 2005).

QF2b. Does this chapter provide an adequate overview of key lead-related health effects? Are the key summary statements and conclusions regarding the effects of lead on various organ systems sufficiently substantiated by the assessed epidemiologic evidence?

Yes.

QF2d. Drawing causal inferences between increased lead exposure and adverse health effects in epidemiologic studies is complicated by the presence of many potential confounders that may both affect lead exposure and be associated with the health outcome of interest. Is the discussion of the various potential confounders of lead health effects adequate? Given the concern regarding the influence of such confounders on the effect estimates, are the stated key conclusions regarding lead effects on various health outcomes appropriate?

Yes. The discussion was clear and appropriate. The conclusions were justified.

One option to further address potential confounders would be to incorporate more of the relevant toxicological data from animal studies, but these studies should be described in Chapter 5.

One additional point that is worth describing is how other "unknown or unmeasured confounders" may or may not account for the findings at lower levels of exposure. In general, children who have lower blood lead levels also have fewer environmental insults (e.g., less tobacco exposure, more nurturing home environment) that act as confounders than children with higher blood lead levels. Yet the greatest decrements per unit increase in blood lead levels were observed in this "low-risk" group. Although other types of confounders may be at play, do the authors think this minimizes the problem of unmeasured confounders?

QF3. Discussions of epidemiologic studies mainly focus on studies of potential lead effects among infants, school-aged children, the general population, and occupationally-exposed populations. Some studies also examined potentially susceptible individuals such as those with chronic medical diseases and specific genetic polymorphisms. Does Chapter 6 adequately cover key populations that should be considered for present purposes? Are the discussions of differences in individual vulnerability and susceptibility adequate?

Given that there is limited evidence of individual susceptibility, the review is adequate.

Other Comments:

Page 6-50, lines 25-27: It is also worth pointing out that, in addition to other sociodemographic factors, the observed lead effects vary because the mean blood lead concentrations differ among the various cohorts. The two prospective studies with the lower mean blood lead levels exhibited the steepest IQ-blood lead slope, despite representing two distinct subpopulations (Lanphear, 2005).

Page 6-68, lines 10-12: As written, the reader might assume that the primary analysis of the pooled analysis was a random-effects model. The random effects model was done as a secondary analysis to test the stability of the main (fixed effects) model.

Page 6-91, line 27: There is a typo. "101 μg/dL" should be "10 μg/dL".

Page 6-225, line 27: I was a bit surprised at the levels the writer considered "relatively low." Is there any reason to speculate that, consistent with the new findings for the lead-IQ relationship, that the absence of consistent associations with reproductive outcomes is because most studies only examined women with higher blood lead concentrations (i.e., there was no true control group)? This should be considered in the summary.

Page 6-227, line 31: In the review on lead exposure and low both weight, the author concludes that the existing studies "adequately measured exposure". It may be prudent to consider whether a single blood sample – whether it was cord blood or maternal blood – is "adequate" for reproductive outcomes. What are the correlations of serial blood lead levels taken serially during pregnancy? Is exposure misclassification a potential problem? What about timing of the measure of lead exposure during pregnancy?

Page 6-233, lines 6-30: The summary should include some discussion about exposure misclassification, particularly because most of the existing studies relied on a single measure of blood lead (cord or maternal) to estimate lead exposure.

Additional Comments of Bruce Lanphear, M.D. [BL] (dated 4/13/2006)
Addressing Comments of Michael Rabinowitz, Ph.D. [MR] (dated 4/11/2006)

Additional Comments on the 1st Draft Lead AQCD by Michael Rabinowitz, Ph.D. [4/11/2006]

Mike's comments are in bold, followed by my reply.

MR: I want to express my concern that the issue of confounding of lead's effects on child development, as they appear in the section on the epidemiology of lead's impact on human health are not fully developed or adequately explored.

BL: I am quite comfortable with Mike's proposal to augment the discussion of confounding, but it should be balanced. If we discuss the issue of confounding, we should also discuss the likelihood that we are underestimating lead's true effect by including iron status and the HOME Inventory. The HOME Inventory is an index of the child's environment constructed using a variety of variables, including housing condition. Housing condition is highly correlated with lead exposure.

One additional point that is worth describing is how other "unknown or unmeasured confounders" may account for the findings at lower levels of exposure. In general, children who have lower blood lead levels also have fewer environmental insults (e.g., less tobacco exposure, more nurturing home environment) that typically act as confounders with lead exposure and IQ scores. Yet the greatest decrements per unit increase in blood lead levels were observed in this "low-risk" group. Although other types of confounders may be at play, these results reduce the problem of unmeasured confounders.

Two of the variables that people often raise questions about as unmeasured confounders that have not previously been accounted for in the lead literature are breastfeeding and mouthing behaviors. Although one can argue that mouthing behaviors are on the causal pathway, we explored whether these two variables acted as confounders or altered the results of the Rochester Lead Study. In unpublished analyses, we showed that breastfeeding and mouthing behaviors were not confounders nor did they change the results of the study.

Finally, the available evidence suggests that a relatively small number of variables (e.g., HOME score, SES, birthweight and maternal IQ) are the primary confounders of the lead-IQ relationship and that including other variables does not appreciably change the estimated lead effect (Tong, 2000; Bellinger, 1992; Canfield, 2003; Lanphear 2005).

MR: Unlike most other environmental pollutants, lead's effects, as we encounter them, are strongly confounded by other risk factors. The extent of this confounding varies among the populations studied, depending on the patterns of lead exposure in the particular circumstances. For example, is lead exposure correlated or not with social class or family income.

BL: My impression is that, more often than not, environmental pollutants concentrate among impoverished communities or minority populations. This is true for biomarkers of tobacco exposure, mercury and PCBs – all of which are more heavily concentrated in African Americans (CDC, 2005). The effects of these toxicants on various outcomes would probably be strongly confounded by other risk factors. In some cases, these environmental pollutants may actually *explain* health disparities that are too often blamed on generic surrogate markers such as socioeconomic status.

It is worth noting that the two prospective studies with the lowest mean blood lead levels exhibited the steepest IQ-blood lead slopes, but represented two distinct subpopulations (the Boston Study, which was largely White, middle-class families and the Rochester Study, which was largely African American, lower income families) (Canfield, et al. 2003; Bellinger, et al. 2003).

MR: It is worth remembering that lead's effects are small, only a few IQ points, typically, compared to other much stronger determinants, such as parental education or family income. This is especially true at the lower blood lead levels currently being explored, now typically below 10 µg/dL.

BL: I am always surprised by the interpretation that the effects of lead are "small." Although I wasn't involved in lead research during the 1980s, my understanding is that it was commonly argued that "the effects lead were small or non-existent". Yet during the past three decades children's mean blood lead levels declined from 15 µg/dL to 2 µg/dL. The data indicate that the impact of this decline in blood lead levels is quite substantial, perhaps by an average of 5 or more IQ points.

For contemporary children, a 4 to 7 IQ point decrement is associated with a 10 µg/dL increase in blood lead concentration (Lanphear, 2005). On a population level, these subtle deficits are actually quite substantial. Landrigan and others estimated that the annual cost of lead poisoning in US children was $40 billion per year -- which is more than the NIH's annual budget (Landrigan 2002). Landrigan used a 2.5 IQ point decrement for the first 10 µg/dL increase in blood lead concentration, which is an underestimate (see Figures 1-2).

This argument - that the effects of lead are small - also ignores other adverse effects of lead, from cardiovascular disease to tooth decay and criminal behavior. Although these other effects are not as extensively studied as lead's effect on IQ, they raise further questions about our tendency to underestimate the overall effect of lead on human populations. There are two (unpublished) prospective studies that confirm prior studies implicating childhood lead exposure with criminal behavior and dental caries. The first shows that childhood lead is a predictor of criminal arrests and, for males, incarceration. The second study shows that childhood lead exposure is a risk factor for tooth decay. Thus, while the effects of lead on an individual are subtle, the existing literature indicates that the effects are quite substantial for several major public health problems.

MR: For me, this is especially potentially troublesome because lead is usually considered as a continuous variable, well measured, while often the other variables may be expressed as categorical variables, so small differences in these factors, when lumped into the same category, cause differences in the outcome which could be ascribed to lead. For example, if the mother graduated only 8th grade or 9th or 10th, they could all be scored as not graduating high school. I do hope my concern about this is unfounded, and closer examination will show me worried needlessly.

BL: I doubt that there is anything I can do to convince Mike that he is worrying needlessly. On the other hand, we could test some of your questions using the pooled data set if it would be valuable to the Committee. In contrast with Mike, I am actually quite surprised that the studies show considerable consistency after adjusting for confounders, despite substantial differences in the sample characteristics and measurement error.

MR: As I tried to explain, I think these circumstances require us to look at each of the studies to examine the extent of the confounding. For example, in a given study, the model predicting IQ as an outcome, can be made with and without a lead term; and then seeing if adding the lead term (and the additional degree of freedom) statistically-significantly improves the model's goodness of fit. This would tell us if lead is an independent risk factor. Also, examining the effect of adding the lead term on the regression coefficients of the other terms would tell us in a quantitative way the extent of the confounding in that population. For example, does the coefficient for parental education change significantly when the lead term is added. In this way we can see how free the lead effect is from confounding, and hence how reliably the lead effect was measured in that study. This would enable us to put more weight on studies where lead's effects were more cleanly measured.

BL: As promised, we prepared the attached table at Michael's request (Figure 3). One of the difficulties with Michael's request is that maternal IQ (which he requested at the meeting) is acting as a confounder (i.e, alters the lead coefficient by > 10%) in *every* prospective study. I also attached a slide with unadjusted estimates and estimates adjusted for HOME Score, maternal IQ, birth weight and maternal education (Figure 4). The reason we only adjusted for HOME score, maternal IQ, maternal education, and birth weight in Figure 4 should be evident by examining Figures 5 and 6. We could explore Michael's new questions using the pooled data set if it would be useful to the Committee. I could also write up our analysis exploring breastfeeding and mouthing behaviors as confounders. In the meantime, I attached several tables from the pooled analysis that we conducted to understand the extent of confounding (Figures 2-6).

References:

Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 1992;90:855-61.

Bellinger DC, Needleman HL. 2003. Intellectual impairment and blood lead levels. N Engl J Med 349:500-502.

Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N Engl J Med 348:1517-1526.

Centers for Disease Control and Prevention (2003) Second national report on human exposure to environmental chemicals. Atlanta: National Center for Environmental Health. NCEH Pub. No. 02-0716. 257 p. Available: http://www.cdc.gov/exposurereport/2nd/pdf/secondner.pdf.

Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL. 2001. Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 23:511-518.

Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environ Health Perspect 2002;110:721-728.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J. Low-level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis. Environ Health Perspect 2005;113:894-899.

Moss ME, Lanphear BP, Auinger P. 1999. Association of dental caries and blood lead levels. JAMA 281:2294-2298.

Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK. 2003. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA 289:1523-1532.

Needleman HL, McFarland C, Ness RB, Fienberg SE, Tobin MJ. 2002. Bone lead levels in adjudicated delinquents. A case control study. Neurotoxicol Teratol 24:711-717.

Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. 1990. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. N Engl J Med 322:83-88.

Schwartz J. Lead, blood pressure, and cardiovascular disease in men and women. Environ Health Perspect. 1991;91:71-75.

Schwartz J. Lead, blood pressure, and cardiovascular disease in men. Arch Environ Health. 1995;50:31-37.

Tong S, Lu Y. 2000. Identification of confounders in the assessment of the relationship between lead exposure and child development. Ann Epidemiol 11:38-45.

Figure 1: Estimated Lead-associated IQ Deficits by Concurrent Blood Lead Concentration

Range of Blood Lead	Estimated IQ Deficit (95% CI)
< 1 to 30 µg/dL	9.2 (5.7, 13.1)
<1 to 10 µg/dL	6.2 (3.8, 8.6)
10 to 20 µg/dL	1.9 (1.2, 2.6)
20 to 30 µg/dL	1.1 (0.7, 1.5)

Figure 2: Estimated Lead-associated IQ Deficits by Blood Lead Concentration, 5th to 95th percentile

Range of Blood Lead	Estimated IQ Deficit (95% CI)
2.4 to 30 μg/dL	6.9 (4.2, 9.4)
2.4 to 10 μg/dL	3.9 (2.4, 5.3)
10 to 20 μg/dL	1.9 (1.2, 2.6)
20 to 30 μg/dL	1.1 (0.7, 1.5)

Lanphear BP, et al. EHP 2005;113:894-899.

Figure 3: Linear Relationship of Full Scale IQ and Concurrent Lead by Individual Cohort

Cohort N=1333	Unadjusted		Adjusted for Maternal IQ*	
	β (S.E.)	P	β (S.E.)	P
Boston	-0.97 (.34)	.006	-0.85 (.33)	.012
Cincinnati	-0.45 (.14)	.004	-0.32 (.14)	.021
Cleveland	-0.82 (.19)	<.001	-0.54 (.19)	.006
Mexico City	-0.02 (.23)	.946	0.14 (.22)	.516
Port Pirie	-0.58 (.13)	<.001	-0.26 (.12)	.031
Rochester	-1.45 (.29)	<.001	-0.94 (.27)	<.001
Yugoslavia	-0.11 (.06)	.046	-0.14 (.05)	.006

Figure 4: Linear Relationship of Full Scale IQ and Concurrent Lead by Individual Cohort

Cohort	Unadjusted		Adjusted*	
	β (S.E.)	P	β (S.E.)	P
Boston	-0.95 (.34)	.006	-0.61 (.34)	.075
Cincinnati	-0.39 (.14)	.004	-0.25 (.14)	.089
Cleveland	-0.82 (.19)	<.001	-0.24 (.19)	.209
Mexico	-0.02 (.20)	.914	0.16 (.22)	.465
Port Pirie	-0.62 (.11)	<.001	-0.13 (.13)	.305
Rochester	-1.42 (.28)	<.001	-0.80 (.28)	.005
Yugoslavia	-0.11 (.05)	.038	-0.14 (.04)	.002

* Adjusted for HOME score, maternal IQ, maternal education, and birth weight

Figure 5: Univariate Relationship of Full Scale IQ to Individual Covariates, Controlling for Site

Covariate	β	p value
HOME Score	7.31	<.001
Maternal Education	4.45	<.001
Maternal IQ	7.85	<.001
Birth Weight	2.01	<.001
Birth Order	-1.38	<.001
Maternal Age at Delivery	0.99	0.008
Child's Sex	0.58	0.394
Prenatal Smoking (Y/N)	-2.20	0.006
Prenatal Alcohol (Y/N)	1.16	0.20

Figure 6: The Relationship of IQ vs Selected Blood Lead Indices Adjusted for All Available Covariates

Variable	Concurrent (R^2=0.630)		Peak R^2=0.628)		Early Childhood (R^2=0.631)		Lifetime Average (R^2=0.629)	
	β	p value	β	p value	β	p value	β	p value
log blood Pb	-2.58	<.001	-2.79	<.001	-2.09	0.001	-2.97	<.001
HOME Score (z-score)	4.23	<.001	4.30	<.001	4.32	<.001	4.28	<.001
Maternal IQ	4.77	<.001	4.88	<.001	4.98	<.001	4.88	<.001
Maternal education	1.12	0.016	1.14	0.014	1.17	0.012	1.11	0.017
Birth weight (per 100 g)	1.53	<.001	1.53	<.001	1.48	<.001	1.51	<.001
Birth order	-0.44	0.275	-0.44	0.275	-0.46	0.252	-0.44	0.275
Child's Sex	0.46	0.486	0.46	0.489	0.44	0.511	0.46	0.493
Marital status	1.15	0.259	1.00	0.328	1.10	0.437	0.99	0.333
Maternal age	0.13	0.768	0.18	0.675	0.21	0.761	0.17	0.701
Smoking (Y/N)	-0.08	0.915	-0.06	.938	0.03	0.974	-0.05	0.947
Alcohol (Y/N)	0.74	0.401	0.40	0.707	1.08	0.227	0.81	0.361

Dr. Samuel Luoma

February 27, 2006
To: Rogene Henderson, CASAC Chair; Fred Butterfield, CASAC Federal Officer
From: Samuel N. Luoma, US Geological Survey

Subject: Review: Chapter 8

General Comments: The document does cover a wide range of topics with regard to aquatic and terrestrial effects of lead. But much of the review leaves the perception of a preliminary draft. Chapter 8 has many redundancies and, more important, insufficient synthesis. Nor does it yet focus on the aspects of Pb in the environment that are most relevant to atmospheric deposition. I am not sure that Chapter 8 yet meets the objective cited in our charge materials (italics are mine): "The purpose of the Lead AQCD is to provide a *critical assessment* of the latest available scientific and technical information in peer-reviewed published literature … effects associated with the presence of lead in the ambient air". …. "emphasis is placed on *interpretative evaluation and integration of evidence* in the main body of the document"

Specifically:

1. The document recites findings in a selected literature. But it is not a critical assessment, an interpretive evaluation or an integration of evidence. One way to begin to meet these goals could be inclusion of an explicit conceptual model for how Pb in ambient air might affect aquatic/terrestrial ecosystems. No integrative concept is presented verbally or as a simple model. For example, such a model could show how various processes are integrated: sources>concentrations>speciation/form>pathways of exposure>processes affecting bioavailability via each pathway>internal accumulation by different components of the food web>role of detoxification or resistance>toxicity> adverse effects at the population/community level>roles of food webs.
2. The document often falls short of clearly discussing how behavior and effects of Pb differ from other metals. Pb is clearly different in terms of sources, processes determining environmental concentrations, dispersal, pathways of exposure, what organisms are most likely to be affected etc. Where data is missing for Pb, specifically, it could be highlighted.
3. The document does not focus in on how atmospheric sources might differ in their impacts from other sources. Physicochemical form of inputs could be better considered. Most important, however, is the type of systems that are vulnerable to atmospheric inputs: lakes (especially pristine lakes) should be of special concern; coastal zones and even the open ocean are known to show anthropogenic signals from increased Pb use. The document should help us understand what is known about Pb in those ecosystems, and where data is missing.
4. The document does not help us understand what types of organisms might be most affected by Pb and why. It presents an uncritical citation of selected toxicity studies, but does little to pull these data together with more biologically-specific information. Metal contamination eliminates some species while others survive. Understanding even a few basic things about which are which could be quite helpful. For example, are higher

trophic level organisms more or less vulnerable to Pb exposure than lower trophic levels, and why (e.g., Settle and Patterson [?] did some work on this in the 1970s). Are phytoplankton/plants more likely to be affected before invertebrates? Can we judge this from existing literature, and if not, why not?

5. Less important, Chapter 8 is kind of irritating in the way it is written. Subject areas, citations and even full paragraphs are repeated, sometimes more than twice. It could be cut by ½ with no loss of content.

Some individual topics are well covered, including analysis of limits to the state of knowledge. Examples are dissolved speciation of Pb and acute toxicity from dissolved exposures. There is some synthesis of ecosystem effects observed in field studies, although the tone of these sections is not especially constructive. But important topics are incomplete in their analysis. For example:

1. The section on Pb concentrations in surface waters is especially incomplete. The authors of some of the early chapters in the review taught us that Pb concentrations are very low in natural waters, if exacting sampling/analytical protocols are followed. Most numbers on Pb in water are wrong, in fact. In Chapter 8, the NAWQA database is the only literature used to evaluate Pb in natural waters. Lead analyses from its predecessor (analyses in the same laboratory), the NASQUAN database, were thoroughly discredited in the published literature in 1991 (15 years ago). As a result the NAWQA analyses have very high detection limits (as the document notes, 86-88% of data are below detection). Furthermore these data are all from streams and rivers, where direct atmospheric sources are not as important as in lakes. NAWQA data (from my own agency, I might add) are therefore not especially informative (and perhaps even a little suspect) for understanding relevance of atmospheric Pb to the aquatic environment. There are many analyses from the sea and some studies of lakes (e.g., Nriagu et al's study of the Great Lakes circa 1996) in the published literature, that are done by reliable laboratories. But literally none of these are reported. The failure of USEPA to note the analytical challenges of determining lead in natural waters is also a serious omission. Finally, by mistakenly leaving the impression that Pb occurs in µg/L concentrations in natural waters, the report disguises the important discrepancy between Ambient Water Quality Criteria and real world concentrations.
2. Three bioaccumulation strategies are cited (first on p 8-121) "for lead". There is no evidence of strategy 2 or 3 for lead that I am aware of (and none cited in the document). This concept applies to all metals. Pb is distinct in its typical strategy (type 1). There are no uptake rate or loss constants given for Pb; so no coherent analysis of such data is possible from the report. If such data do not exist it should be explained why. In general the bioaccumulation section needs to be better integrated with toxicity and detoxification.
3. The absence of critical evaluation in key places leaves a perception of unbalanced analysis of some important issues; and leaves, un-discussed, contradictions that could be critical to managing Pb contamination.
    a. As mentioned above, Ambient Water Quality Criteria for Pb are in the µg/L range; but Pb in natural waters probably never reaches such concentrations except where near mining activities. Does this mean there are not adverse effects in nature? Are the studies of Pb effects in ecosystems consistent with that? Or does

it mean we should take a new look at chronic Pb effects in light of what chemical advances have taught us about Pb concentrations in the real world.

b. The BLM model is mentioned many times in both the terrestrial and aquatic sections. There is no BLM model for Pb, as the document notes in one place. There are also serious limitations to application of the BLM for managing aquatic contamination, at the present state of knowledge. The discussion of this concept is overly optimistic and incomplete. Some balance is needed.
c. BCFs and toxicity tests are cited, with no discussion of why there is such immense variance in both. Some discussion of why Pb toxicity varies from 0.45 µg/L to 1000's of µg/L warrants some attention. The USEPA Metals Framework sees only limited uses for BCF's, but that is not mentioned that I saw.
d. There is literally no discussion of dietary exposure to Pb in the aquatic section; or trophic transfer. The quantitative importance of dietary metal exposure has now been well established for ~10 years. It is mentioned twice in passing but never taken seriously. If the data is not available that should be noted.
e. Recommended protective values for Pb in soils and sediments vary quite widely, illustrated in the tables in this chapter. The statistical approach is examined only to state that bioavailability is not considered, then it is dismissed. This approach has advantages (and disadvantages) that govern where and when it is useful. Those are not discussed. The equilibrium partitioning approach, on the other hand, is discussed, several times, in much more detail, but with no consideration of any limitations. For example, the behavior of sulfides is critical to this approach but is never mentioned (an entire issue of *Marine Chemistry* was devoted to this in the last few years, but is not cited). There is no indication of the scientific furor over the applicability of the SEM-AVS approach in natural settings (e.g. related to instability of AVS, vertical and spatial variability in AVS, dependence of results on sampling protocols, role of dietary exposure, role of experimental protocols like homogenization of sediments, difficulty of relating geochemical sampling to what organisms actually experience). A balanced document should give the reader some sense of this debate.

In its incomplete state, Chapter 8, as it stands, will be of marginal value in helping consider the aquatic environment when deriving air quality standards for lead. The chapter needs to be completed. That should include a balanced analysis for all topics, explicit consideration of where lead falls in the spectrum of processes that govern metal effects in the environment, and explicit consideration of how such processes/principles apply to regulating atmospheric inputs of Pb to the aquatic environment.

Dr. Frederick J. Miller

Fred J. Miller, Ph.D.
February 21, 2006

Chapter 4. Models of Human Exposure that Predict Tissue Distribution of Lead

General Comments

The author(s) of this chapter have captured the basic information needed to understand the strengths and weaknesses of the various dosimetry models for lead in humans incorporating the oral, dermal, and inhalation routes of exposure. The text is well written and easy to follow. Currently missing from the chapter is "a bottom line" as to which model or models the author(s) feel would be the most appropriate for use in the assessment of potential risks in humans from exposure to lead. In addition, a lot of information on model parameter values and variables that is stated to be available would be well suited to include in an Annex chapter. Specific comments listed below address the need for technical clarifications or the need to address certain topics or questions.

Specific Comments

p. 4-3, l. 12	This sentence about large uncertainty being expected to remain is an overstatement. One is better off identifying the uncertainties and then using sensitivity analyses and probabilistic methods to quantify their impact.
p. 4-4, l. 25	Personally, I do not like calling models by the developer's name. The model on this page was developed by Rabinowitz – it is not the Rabinowitz Model.
p. 4-7, l. 4	Is the assumption that the central compartment is 1.5 times the volume of whole blood a reasonable one?
p. 4-10, l. 5	The fact that the O'Flaherty and Leggett models do not specifically state lead exposure patterns is not a drawback. Moreover, the author states the IEUBK model includes parameters for handling exposure, but how good are they?
p. 4-10, l. 14	Provide a reference that applications in risk assessment typically require models that accurately predict blood lead distributions in the upper tails of the distribution. One is usually limited by the availability of experimental data to evaluate the reasonableness of model predictions.
p. 4-13, l. 13	Why assume that 32% of the inhaled lead is deposited in the respiratory tract? One can use any one of a number of models to estimate this amount – e.g., ICRP or the Multiple Path Particle Dosimetry Model available from CIIT Centers for Health Research.
p. 4-13, l. 19	The assumption that lead deposited in the alveolar region is completely absorbed from the respiratory tract is simply not valid. Macrophage mediated clearance removes a large amount to the G.I. tract absorbs about 30% of this amount.

p. 4-13, l. 30	A reference should be provided for the reasonableness of the assumption that blood lead concentration at birth is 0.85 of the maternal blood lead.
p. 4-15, l. 13	How reasonable is it to assign the two bone compartments identical rate coefficients for transfer of lead from bone to plasma-ECF?
p. 4-17, l. 5	The authors should describe what percent the value of 0.7 µg/dL distance from the geometric mean represents as a percentage of the mean.
p. 4-18, l. 12	Remove the duplicate "for estimating"
p. 4-18, l. 26	This is a QA exercise and not a model validation or verification.
p. 4-21, l. 18	Where do the t ½ values come from? Estimated from data?
p. 4-22, l. 17	The authors should provide a cross reference to Chapters 2 & 3 where airborne concentrations of lead are discussed.
p. 4-29, l. 27	Of the EPA All Ages Lead Model is currently under development, why is it presented here? The model should be published in the peer reviewed literature before being used in "prime time". Why does the model stop at 90 years of age?
p. 4-37	Do the authors have an explanation for why the Leggett model consistently predicts higher blood levels than either the O'Flaherty or IEUBK models? Which predicts are closest to any available experimental data?

Dr. Paul Mushak

USEPA's FIRST AQCD EXTERNAL REVIEW DRAFT: PRE-MEETING REVIEW COMMENTS AND RESPONSES TO THE PANEL'S CHARGE

Reviewer: Paul Mushak, Ph.D.

I have a number of general and specific comments. General comments address the organization of the draft and its chapters, the rationale for the organization and chapter composition, and conceptual issues underpinning the updating since 1986 (in some instances since 1990). The specific comments are assembled with reference to charges to the Agency's Panel and stay as much as possible within the overall topics contained in the Agency's 2/15/06 Charge questions to the panel.

Comments are guided by perspective and experience with the preparation of numerous Federal, international and NAS/NRC expert consensus documents as either coauthor or as a review panel member/chair. Particular guidance for this Pb draft AQCD is provided from coauthorship of multiple sections of two previous EPA lead criteria documents, those issued in 1977 and 1986. Comments on Chapter 4, the predictive models of body lead burdens in various age groups, are guided by membership on the SAB review panel for EPA's All Ages Lead Model, an independent effort.

I. OVERVIEW AND OTHER GENERAL COMMENTS

A. Overall Draft Pb AQCD Quality, Thoroughness and Organization of Chapters

This draft is an enormous and generally well-done effort with respect to an objective reckoning for the material that's out there. The count is 1743 pages (v. I + II) without the missing Chapter 7. It is especially noteworthy given the time constraints under which the Chapters were done. The Agency and its authors plus reviewers are certainly to be commended for the scope and interpretive depth of the draft.

Lead research and the resulting global lead literature are seemingly continuous processes. No critical assessment of this ongoing process or "moving target" by any body of scientists and policy makers can ever be 100% complete in the dimensions of time and space. Rather, one uses a selective process of choosing the most well done, the most vetted and the most relevant studies for evaluation. The EPA has generally hewed to this prioritizing in assembling this first review draft. NCEA/EPA has done this in two ways in term of format. First, there was a focus on the main data base and its placement in Volume I. Second, more details and data of an archival nature were placed in Volume II. The evaluation process at a later administrative and programmatic step is further filtered through the statutory mandates and regulatory needs of the Agency.

Purpose of the Updating

The updating rationale was reasonably well presented in Chapter 1. However, that text dealt largely with its focus on the broad statutory and regulatory requirements of EPA. There are

requirements for updating in any expert consensus document for lead that are peculiar to lead. This aspect of the preamble could perhaps be an early part of the integrating synthesis chapter, Chapter 7. Present place-holder Chapter 7 should actually be Chapter 8, with the Environmental Effects being the wrap on the supporting Chapters. The Environmental Effects chapter should not be editorially presented as a categorical afterthought to the main document. More on this is offered below.

Lead as contaminant and toxicant differs from many other contaminant substances within a clinical medical and risk assessment framework. That is, lead not only produces risk of disease as some probability within a dose/exposure-driven epidemiological and statistical significance framework, but also produces actual and identifiable disease which stratifies into symptomatic/ clinical or asymptomatic/subclinical categories.

It is useful to keep in mind that, before the first modern epidemiological studies of lead impacts were ever published, around 3,000 papers had been published in the global literature on clinical lead poisoning and clinically toxic occupational and nonoccupational lead exposures by the early 20th Century (Blansdörf, as cited in Fee, 1990 and analyzed by Mushak and Mushak, 2000). This reviewer also noted (Mushak, 1992) that in 1991 there were over 1200 entries in *Chemical Abstracts* on lead toxicity, lead exposure and lead laboratory measurement. There was in 1991 over 400 entries in *Index Medicus* for mainly human lead exposure and poisoning. Over 600 entries for mainly experimental lead toxicity studies appeared in the 1991 *Biological Abstracts.*

Fee E. 1990. Public health in practice: An early confrontation with the 'silent epidemic' of childhood lead poisoning. J. Hist. Med. 45: 570-606.

Mushak P, Mushak EW. A comparative analysis of the evolution of lead and mercury as public health hazards. In: 11th International Conference on Heavy Metals in the Environment (J. Nriagu, ed.). CD-ROM: Manuscript No. 1445. University of Michigan, Ann Arbor, MI, August 6-10, 2000.

Mushak P. 1992. The landmark Needleman study of childhood lead poisoning: Scientific and social aftermath. PSR Quarterly. 2: 165-170.

The 1977 lead criteria document dealt largely with manifested disease, overt lead poisoning. That is, the human impact portions of the 1977 document were guided by the traditional medical model of physician and patient, presenting the upper end of the full lead dose-toxic response relationship. However, some of the earlier studies in asymptomatic children, i.e., studies placed lower on the dose-toxic response curve and yielding to more of a public health risk or preventive medical model, received some discussion. The mix of dose-response data for purposes of risk assessment was presented in Chapter 13 of the 1977 document. The 1977 document was the first to identify the fetus and young children as the subsets at special toxicity risk from lead. Young children were then considered as the target group for protection from lead exposure in formulating the 1.5 $\mu g/m^3$ air Pb Primary and Secondary NAAQS in 1978.

The four-volume 1986 AQCD, the 1986 Supplement and 1990 Addendum collectively had much to say about clinical lead poisoning but also included much more published data from the global literature on sub-clinical lead toxicity. The clinical and public health models were more equally represented. The latter evolved in concert with evolution of more sophisticated tools to identify increasingly more subtle toxic endpoints. Many of the target organs and systems for lead toxicity as now understood to comprise the corpus of lead's toxic injury, including the critical effect of developmental neurotoxicity in young children, were at least in place in the 1986 AQCD, the 1986 Supplement, and the 1990 Addendum. In the case of developmental neurotoxicity, cross-sectional studies and the earlier epidemiological data generation from the prospective studies were becoming available.

Lead as contaminant and toxicant also differs from virtually all other toxic contaminant substances in the nature and amount of solid scientific evidence establishing the substance as a very toxicologically potent contaminant. The three pillars of evidence are mechanistic, experimental and epidemiological. Very few environmental contaminants answer in the affirmative to as many of the criteria questions for entrance to causality posed by A. Bradford Hill in 1965.

To date, the various mechanistic and experimental studies on lead are in full accord with the evidence continuously forthcoming from human population studies. To date, the various mechanistic and experimental studies keep showing more robust dose-response relationships in lock-step with the most recent environmental epidemiological studies. The direction of findings continues to be down the dose-response curve. That is, lead continues to be more potent and more varied in this increased potency than we had assumed. One need only have a comparative look at the dose-response data for developmental neurotoxicity and the robust data for the newer field of childhood Pb immunotoxicity in the current Pb AQCD. I am not aware of any body of scientifically credible empirical studies of the critical adverse effects of lead and done by credible scientists that has posited the argument that lead is much less potent toxicologically than we had assumed.

Given the above historical and contextual points, a critical review of the current Pb AQCD would entail looking for known developments in the lead field relevant to lead toxicology and lead exposure assessment and regulation:

--Newer data since 1986-90 identifying more precisely the shape of the lead dose-response curve in both human and non-human populations for known somatic targets of lead in vulnerable segments of populations;

--Newer data identifying toxic effects of lead in those organs and systems that were only first being recognized or were not recognized at all as targets for injury in the 1986/90 documents;

--Newer methodological and interpretive tools that permit a fuller and more transparent elaboration of more effective assessments of strategies within lead regulation and public health policies. Overall, the updating draft AQCD for lead has done a reasonably good job in providing the above.

Organization and Quality of the Chapters

I don't quite understand the placement of "Environmental Effects of Lead" in this updating AQCD draft as Chapter 8, after any synthesizing-of-the-material. It really ought to go as Chapter 7 and the wrap Chapter 7 should then become by definition the last chapter. The synthesizing chapter, when written, should of course include a section for environmental effects. Environmental effects, ecotoxic effects, or whatever the vocabulary applied here, are not inconsequential. They provide the wherewithal for the secondary NAAQS and also are intimately connected to human impacts in a holistic way such as to define lead as a biospheric pollutant.

EPA and CASAC clearly consider the environmental effects important. The page count and subject matter coverage in this draft is much more than in the respective sections in the previous criteria documents. CASAC obviously considers the Chapter as significant, having assigned more reviewers (five) to this section than any other in the draft. Secondly, a number of the Chapters serving as prelude to the human impact chapters, i.e., Chapters 2 and 3, are also critical to environmental effects. For example, lead emissions, lead fate and transport, lead in environmental media, are equally important to all receptors. Air lead deposition into terrestrial and aquatic systems covered in current Chapter 8 is simultaneously a major conduit for pathways of childhood lead exposure via leaded dusts and soils.

Whither Chapter 7?

I understand the role of this CASAC/SAB panel to be the usual one: to review the scientific quality and validity of the material as prepared by EPA in this first draft AQCD for lead. EPA presents and CASAC proposes. That being the case, the absence of a first-draft integration and synthesis Chapter leaves the panel in the dark as to what is EPA's take on all the information. I can certainly understand that time was in increasingly short supply as the writing of this draft proceeded. That was pointed out.

As I understand the planned preparation of a wrap chapter, this will be done post-first meeting and presented for separate review at a second meeting. There is some logic in having the Agency prepare a synthesizing integration chapter from individual sections each of which have already been evaluated by the CASAC panel. There are worse things for agencies nowadays than paying attention to scientific advice more than once.

Some might argue that a first-draft synthesis could have been attempted between the December 1 posting on the internet and the circulation of the chapters to the review panel. I would argue that a hasty effort would represent little additional progress.

Prior incarnations of EPA's Lead AQCDs did not present this kind of problem and some value may attach to looking at some of the thinking that went into the wrap chapters in those documents. The 1977 document had a synthesizing Chapter 13 prepared and reviewed with the other 12 Chapters by the then-extant CASAC committee twice: June, 1977 and October, 1977.

The four-volume 1986 Lead AQCD had two layers of overall assessment and synthesis, all presented simultaneously with the other Chapters to the then-extant CASAC committee. The principal synthesizing Chapter was Volume I, Chapter 1 "Executive Summary and Conclusions" that consisted of 198 pp. and a 67 pp. Appendix. A shorter, more focused Chapter 13, Volume IV, 54 pp, contained an overall summary of data "EVALUATION OF HUMAN HEALTH RISKS ASSOCIATED WITH EXPOSURE TO LEAD AND ITS COMPOUNDS."

Organization, Variability and Thoroughness Across Chapters

There appears to be considerable variability among the Chapters as to what comprises updating, what's enough information and what's not enough information, what's the level of detail that's appropriate, etc. Presumably, this partly reflects differences in opinion among the Chapter coauthors about the nature and extent of required updating. However, it also clearly reflects the amount of new information. The problem for the latter then becomes one of how much to put in the main part and how much in the archival Volume II.

In many cases, the length of the chapters in this draft update are much longer than they were in the 1986 volumes, meaning that this AQCD is not so much an Addendum as a stand-alone full document. This reflects changes in the size of the data base, even when there is a prioritizing of data that is the most relevant to the eventual regulatory needs of the Agency. The overall length of the sections in Chapters 5, 6, and 8 should not be materially shortened. In some cases, additional text should be added for thoroughness. More about this in specific comments.

In some cases, there appear to be data sets that are both detailed as to clues about molecular and cellular mechanisms but perhaps empirically somewhat remote from impacts of low-level lead exposures at the organismal level. On balance, they should remain for their expository value.

Authors of a number of the Chapters made an effort to clearly interconnect the previous 1986-90 AQCD material with new information, and a number also first provide a summary of what the earlier documents had to say about lead toxicity in this or that organ or system. I would recommend that a standardized format be in place to connect old and new across the Chapters and sections within each Chapter. The proportion old and the proportion new is certainly going to vary across chapters and within chapters. For example, the sections of Chapters 5 and 6 addressing immunotoxicity were quite new, reflecting major advances in the field. The topics were clearly explained and the reader was provided a clear blueprint to go from data to such take-home messages as dose-response relationships and the insidious nature of lead's effects on the immune system.

In some cases, the nature of the new chapters has changed because the contamination and exposure realities have changed. The 1977 and 1986 Pb AQCDs had much to say and analyze about mobile lead sources, i.e., atmospheric contamination from leaded gasoline combustion. That focus has now switched to point sources, keeping in mind that all primary sources of lead past or present have added to pathway reservoirs with long half-lives. In the 1970s, at the time of the preparation of the 1977 Pb AQCD the diet was a significant pathway for lead exposure of children, via a combination of lead-seamed can use and contaminated dietary categories. By the

time of the 1986 Pb AQCD the diet portion of human Pb exposures in the U.S. had declined, based on the FDA surveys such as those of Pennington and Beloian.

The authors of the main human effects Chapters are to be commended for the level of detail about toxicological mechanisms. They were often presented in a way that allows the reader to make sense of the highly diverse phenomenology of lead toxicity. It was also gratifying to see that there was equivalent appreciation among the various authors of the current thinking about certain basic mechanisms associated with lead and other toxicants across organs and systems, e.g., oxidative stress.

The information presented in chapters 5 and 6 also allows the reader to draw comparisons for similarities in responses for lead across organs and systems. For example, it is striking how immunotoxicity and developmental neurotoxicity are largely expressed not at baseline levels of activity but only when exposed individuals are challenged cognitively or immunologically.

Some of the major Chapters are so complete they could serve as an up to date and stand-alone monograph. This specifically applies to Chapter 6, an excellent body of work. All sections were quite impressive in Ch. 6, but the bookending sections, biomarkers of exposure and interpretations of the data, were outstanding.

I found the early, biomarker section of Chapter 6 to be especially clear and well done. The repeated notion here and elsewhere in the draft of an isolated blood lead measurement not being a fully effective marker of lead exposure for certain types of studies was especially gratifying to someone who has been an irritated voice in the wilderness about limitations to single-shot Pb-B screenings on toxicokinetic and other technical grounds:

> Mushak P. 1993. New directions in the toxicokinetics of human lead exposure. Neurotoxicology, 14: 29-42.
>
> Mushak P. 1998. Uses and limits of empirical data in measuring and modeling human lead exposure. Environ. Health Perspect. 106 (Suppl. 6): 1467-1484.

The virtue of serial Pb-B measurements in certain settings is becoming increasingly obvious.

A very good treatment was also done for XRF measurements. The distinctions between methodological and statistical measures of such parameters as detection limits are not easy to explain but a good job was made of it here. There is an interdisciplinary disconnect between the experimentalists in biology and toxicology who use instrumentation characterized by empirically transparent and deterministic detection limits and the data crunchers with a statistical bent, who are not spooked by the notion of calculations from distributions that include negative numbers. A caveat here is that the latter is harder to grasp by the public at large.

Some of the key chapters have gaps. For example, Chapter 6 should have a summary section on dose-response Tables, one for children and one for adults. The Tables would be set forth as they are elsewhere, i.e., thresholds for onset of each adverse effect indexed as Pb-B. These Tables have appeared in earlier EPA documents and documents of other agencies, such as

ATSDR and CDC. One could use shading print for new entries into the Tables from those in the 1986 document.

A second gap is to import the information now in Chapter 5, the Neurotoxicology section, on lead toxicity in individuals versus groups into the appropriate part of Chapter 6. That material is out of place where it now resides and belongs in Chapter 6. As I read that material, there is little that is actually challenging to the material in Chapter 6. Before there were environmental epidemiologists, there were diagnosticians with their clinical takes on bodies of evidence that go into informing a diagnosis.

There were also case reports, case series and clinical epidemiology. CDC Statement risk tables, now partly derived from epidemiological results, are used by clinicians to assist in formulating a diagnosis. CDC does not recommend that an epidemiological study be done for every neighborhood from which an elevated Pb-B index case appears. I don't see the logic of having an important section on what the epidemiological data mean for all aspects of human lead toxicology off by itself.

A third gap at such places as Chapter 6 is insufficient interpretation of some of the findings. For example, the discussion of which of the Pb-B biomarkers – lifetime average Pb-B, high risk age average Pb-B, peak Pb-B, concurrent Pb-B – are more correctly classifying as to the best dose/exposure index needs more elucidation.

For example, it may not be surprising that concurrent or lifetime average are equally robust as the exposure biomarker if the former is largely being determined by the latter, at least in terms of rank ordering. We looked at a five-year follow-up of children's Pb-B levels for a North Carolina exposure group and found highly statistically significant correlation in rank order. We could not discern if the preservation of rank order reflected historical body lead burden input to Pb-B or relative immobility of the children as to residence with resulting continued external lead contacts.

Otto DA, Robinson G, Baumann S, Schroeder S, Mushak P, Kleinbaum D, Baerton C, Boone L. 1985. Five-year follow-up study of children with low-to-moderate lead absorption: Electrophysiological evaluation. Environ. Res. 38: 168-186.

Mushak P. 1989. Biological monitoring of lead exposure in children: overview of selected biokinetic and toxicological issues. In: M Smith, LD Grant, A Sors, eds. Lead Exposure and Child Development: An International Assessment. Lancaster, United Kingdom: Kluwers Academic Press, pp. 129-145.

Chapters in the draft should take cognizance of the fact that, while children's bone lead is quite labile in the first several years of life, bone physiology as described by O'Flaherty at various places favors net bone lead accumulation post infancy. This post-infancy and early toddlerhood onset of bone lead net accumulation is certainly enough that by ages 5 to 7 lead has accumulated.

Germane to the above and for inclusion for discussion is that body lead compartments are all in equilibrium with each other. In particular, bone lead and blood lead are in equilibrium, the k-1 values for lead resorption differing considerably between cortical and trabecular mineral matrix, and between basal states and physiological stress conditions. Existing equilibria are the reason we get "washout" contribution from high bone lead stores newly encountering a central blood compartment with a declining Pb burden owing to reduced exogenous exposures and for stable isotopic mixing where measurable with exogenous lead intakes. Equilibria are also the reason that we find that retired lead workers have their blood lead burden driven by bone lead accumulation, while active lead workers have their Pb-B mainly responding to their real-time exposures.

One gap in current Chapter 8 is little mention even in historical terms of the huge amount of effort that the Federal government put into technical evaluation of the acid precipitation problem and its interaction with toxic metal and metalloidal contaminants. One product of this was a huge interagency study some years ago on the numerous aspects of the acid precipitation problem. That resulted in a multi-volume report that I and others peer-reviewed. Other agencies made periodic reports to Congress, including the National Institutes of Environmental Health Sciences, using peer review reports:

> Goyer RA, Bachmann J, Clarkson TW, Ferris GF Jr, Graham J, Mushak P, Perl DP, Rall DP, Schlesinger R, Sharp W, Wood JM. 1985. Potential human health effects of acid rain: Report of a workshop. Environ. Health Perspect. 60: 355-368.

A clear gap in the document is absence of a full section on the various national and other studies of lead exposures and various correlates thereof. The obvious place for this section is chapter 6, between the discussion of Pb-B and other biomarkers and the organ/system specific human studies of human toxicity. Since the 1986-90 AQCD for Pb, there have appeared NHANES III, Phases 1 and 2, and NHANES IV, with various interim incarnations of the last named over recent years.

Some sections need to keep things in context as to the larger picture for the benefit of the ultimate general reader who is more interested in the regulatory and health policy implications. Chapter 6 describes the international pooled analysis showing a more robust relationship for Pb-B versus cognitive decrement for Pb-Bs < 10 μg/dl versus what's seen at > 10 μg/dl. This is by itself a critical finding, and several reasons for this relationship are discussed in the draft. The curvilinear (downward) relationship of blood-lead and developmental neurotoxicity over the whole dose-response spectrum does not materially affect the fact that, as body lead goes up so does the severity of a particular effect and the multiplicity of effects. The finding of a particularly robust slope size for Pb-B and IQ decrement at Pb-B levels for one segment of the full curve does not mean higher Pb-B values don't also induce robust toxic harm. Pb-B values > 100 μg/dl are still associated with acute and chronic encephalopathy and a significant risk of a fatal outcome. That is, within roughly one order of magnitude of Pb-B values, one goes from risk of subtle neurobehavioral harm to risk of severe, permanent brain injury and death.

II. SPECIFIC COMMENTS AS RESPONSES TO THE CHARGE QUESTIONS

Q A1: To what extent is the draft document format useful and desirable? Can the structure be further improved?

The device of placing support details for major studies in Volume II is logical and should be retained. Reviewers and the interested public may well have questions and differences of opinion from the authors as to what a certain study says or does not say. In those cases, however, the material in Volume II is still available. The size of Volume I with the present arrangement is at the edge of being unwieldy for at least quick review.

Further improvement could include a standard format, as I noted above, of interweaving the 1986-90 documents with the present draft. At present, various authors have dealt with the pre-existing material in quite different and somewhat confusing ways. A good model for this would be a set of bullet statements up front for each Chapter section that concisely captures what was done in the earlier Pb AQC documents.

A second improvement would be more generous use of tables to summarize materials that have only moderately changed since the last documents. This would be helpful for the hematotoxicity portion of Chapter 5.

The document will eventually require an Executive Summary as well as a wrap chapter at the end. Will the panel in the second round of review have an ExSum to look at??

Q B1. Does Chapter 2 provide adequate coverage of important chemical properties of lead...pertinent information on sources of Pb emissions...most relevant data sets...Does the discussion for point and area sources...estimate uncertainties...emissions by key industrial sectors...long-term impact of lead in soils, dusts...

The sections of Chapter 2 are uneven. Part of this has to do with changing exposure and contamination realities. In contrast to what the corresponding sections in the 1986 Pb dealt with, e.g., mobile Pb sources and lead in diet, the current section needs to address point sources, area sources and industrial sector sources. For example, while diet Pb was a factor in discussing lead exposure risks in the 1977 and the 1986 AQCDs, input to today's children's body lead burdens is much less. However, these reductions are for a centralized food supply. The case with ethnic groups using folk diet components and remedies from outside the country for diverse ailments is different, and in U.S. locales where large immigrant populations are clustered, idiosyncratic sources of lead could be more important sources.

The role of lead-laced soils as a continuing localized source is a critical topic for areas where no effective soil and dust lead abatements have occurred. The Chapter discussed this issue in a reasonable way but needed to include more data sets. For example, in Sec. 2.3.3, I don't understand why the 1985 EPA document dealing with fugitive dust emissions was not included. The report, by Cowhert and colleagues from the Midwest Research Institute, is reasonably broad ranging and uses sets of models useful for predicting air lead levels from both aeolian and anthropogenic mobilization mechanisms, e.g., vehicular tires.

Also missing from this section are the various studies of fugitive dust emissions and dusts as a recontamination source at the large Bunker Hill Superfund site. Dr. von Lindern, who has been involved in most of the Bunker Hill studies, will probably have much more to say about what the BH results portend elsewhere.

Also missing from this section are data for tailings piles from mining and milling wastes, which can heavily impact local communities. In the 1970s and 1980s a number of papers appeared by investigators of waste piles in Welsh mining areas.

Davies BE, White HM. 1981. Environmental pollution by wind blown lead mine waste: A case study in Wales, U.K. Sci. Total Environ. 20: 57-74.

Other data sets include those of Van Born et al. and citations contained therein:

Van Born W, Keersmaekers T, Adams F. 1988. Characteristics of resuspended soil particles with high concentrations of Cu, Zn, Cd and Pb as a function of particle size. Aerosol Sci. 19: 1287-89.

The U.S. EPA should have fenceline U.S. monitoring data for point source lead emissions for U.S. facilities subsequent to the 1986 document. The Doe Run smelter in Herculaneum, MO is still operating and several other primary smelters were still operative at the time of the 1986 AQCD and some time afterward. It is a gap in the data in Ch. 2.

Some of the passages in Ch. 2 are either misleading or incorrect and should be clarified or dropped. For example, the first paragraph in 2.3.8 notes that "it is often difficult to determine the original source of an organism's lead burden." It's more often the case that major sources can be identified. One uses conventional exposure assessment methodology within the larger risk assessment paradigms to identify lead sources and pathways. An example is inferential statistical analyses, such as structural equation modeling. One also uses tracers and in some cases ratios of stable lead isotopes.

There are data gaps in Sec. 2.3.7: Plant Uptake. The discussion is mainly focused on root uptake of lead when both foliar and root uptake should be considered. In a number of cases, leafy crops in the proximity of fugitive dust emissions can acquire lead even in the absence of an operating emission facility. The authors should check Chapter 8's parallel section, where foliar uptake is considered in some detail.

Q C1. Does Chapter 3 provide adequate coverage of pertinent available U.S. information on Pb exposure routes..environmental lead concentrations...Does the chapter adequately delineate connections among sources and pathways...Does the chapter adequately identify key sources of information characterizing the level and distribution of lead soil...near roadways...and characterizing "background" levels in urban, suburban, and rural pristine areas?

The Chapter generally provides a set of summaries of environmental lead levels, the interrelationships of one medium to another in terms of the nature and magnitude of lead moving between environmental compartments, etc. However, there are some simplistic statements, some gaps, and some misunderstandings.

One data gap is a set of U.S. studies under the aegis of the National Human Exposure Assessment Survey (NHEXUS) described by Sexton and others in the 1990s. Some of the study results were presented in the Journal of Exposure Analysis and Environmental Epidemiology and elsewhere. The authors should check these out.

Sexton K, Kleffman DE, Callahan MA. 1995. An introduction to the National Human Exposure Assessment Survey (NHEXAS) and related phase I field studies. J. Exp. Anal. Environ. Epidemiol. 5: 229-233.

Pellizarri E, Lioy P, Quackenboss J, Whitmore R, Clayton A, Freeman N, Waldman J, Thomas K, Rodes C, Wilkosky T. 1995. Population-based exposure measurements in EPA Region 5: a phase I field study in support of the National Human Exposure Assessment Survey. J. Exp. Anal. Environ. Epidemiol. 5: 327-358.

Lebowitz MD, OP'Rourke MK, Gordon SM, Moschandreas DM, Buckley T, Nishioka MG. 1995. Population-based exposure measurements in Arizona: a phase I field study in support of the National Human Exposure Assessment Survey. J. Exp. Anal. Environ. Epidemiol. 5: 297-326.

Is there any reason why soil lead levels near mining and related sites are mainly from foreign studies? Table 3.7 shows only two U.S. sites out of 14 presented. There are many more studies out there than given in this Chapter. Furthermore, many of the foreign sites are of more interest for historical reasons than for more current lead exposure assessments. The Portuguese site was mined in Roman and pre-Roman times! Some additional studies should be included. For example, there are those for the Tri-State mining area (MO, OK and KS). Dr. von Lindern can provide separately his list of the Coeur d'Alene River Basin studies, including the Bunker Hill Box site.

Lynch PA, Malcoe LH, Skaggs VJ, Kegler MC. 2000.The relationship between residential lead exposures and elevated blood lead levels in a rural mining community. J. Environ. Health 63: 9-15.

Malcoe LH, Lynch RA, Kegler MC, Skaggs VJ. 2002. Lead sources, behaviors, and socioeconomic factors in relation to blood lead of Native American and White children: A community-based assessment of a former mining area. Environ. Health Perspect. 110: 221-231.

Murgueytio AM, Evans RG, Roberts D. 1998a. Relationship between soil and dust lead in a lead mining area and blood lead levels. J. Exp. Anal. Environ. Epidemiol. 8: 173-186.

Murgueytio AM, Evans RG, Sterling DA et al. 1998b. Relationship between lead mining and blood lead levels in children. Arch. Environ. Health 53: 414-423.

Casteel SW, Cowart RP, Weis CP, Henningsen GM, Hoffman E, Brattin WJ, Guzman RE, Starost MF, Payne JT, Stockham SL, Becker SV, Drexler JW, Turk JR. 1997. Bioavailability of lead to juvenile swine dosed with soil from the Smuggler Mountain NPL Site of Aspen, CO. Fund Appl Toxicol 36: 177-187.

Lanphear BP et al. 1998. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: a pooled analysis of 12 epidemiological studies. Environ. Res. 79: 51-68.

Succop P, Bornschein R, Brown K, Tseng C-Y. 1998. An empirical comparison of lead exposure pathway models. Environ Health Perspect 106(Suppl 6):1577-1583.

The authors should look at some of the studies cited in the Chapter more carefully. For example, the several studies by Mielke and coworkers purporting to show that the principal source of lead in old, inner-city urban areas is gasoline lead have some serious flaws. Most of the flaws have to do with methodology. That is, the study designs favor gasoline lead over paint lead weathering as the lead input source to soils and dusts for these particular inner-city, urban settings.

The evidence for lead paint inputs to dripline soils and soils near property perimeters is solid. When one examines the Mielke studies for stratifying soil lead relative to proximity to the drip line, drip line soils are much higher than soil leads elsewhere. In other cases, the methodology was one of using roadside soil lead as the source variable for gasoline lead input into soil, but using only housing age as the source variable for lead paint. In the Mielke studies, exterior lead paint measurements were not taken for direct environmental lead source comparisons. Without use of exterior paint lead levels and a further variable for lead paint condition, his comparisons are apples with oranges.

Some of the statements in this Chapter with references to inter-compartmental lead movement need to be tightened up. On p. 3-1, the first par., and p. 3-14, top, the statements need clarification. For example, inner-city housing with deteriorating lead paint in the interior and on the exterior can contribute lead to dust by various mechanisms. The series of studies done by the Cincinnati group over the years indicate that inner cities, unlike extractive industry communities, will have contributions to dust lead from both sources. This particular issue of urban lead sources is discussed at some length in EPA's 1996 Integrated Report on the Agency's soil lead abatement demonstration project.

In mining, milling and smelter communities, the case is quite different. There are extensive data showing the significant input of air lead via primary emissions or fugitive dust emissions to soil lead. These yard soil lead inputs produce dust lead, which then determine hand lead and, eventually, children's blood lead.

The authors need to make sure their information is current in all cases. On p. 3-23, 2nd full par., the statement about the primary plumbing solder being 50-50 tin-lead solder seems to be in error. The previous amendments to the Safe Drinking Water Act banned the 50-50 solder

for all public supplies, although presumably rural households on private water sources could still use the 50-50 formulation.

Q D1. How well does chapter 4...characterize key information on...approaches to modeling of external lead exposures and impacts on internal Pb body burdens...status of model evaluation efforts...Does Chapter 4...characterize ability of models to handle the significant factors... Furthermore, does Chapter 4 identify alternative models to the AALM...

The need for modeling of lead exposures as a risk assessment modality of use to the Agency is clear from the potential multi-media nature of lead at particular contamination settings, especially with reference to dust and soil lead sinks that have historically accumulated from historical ambient air lead deposition over the years.

The need for modeling approaches became clear to EPA and its consulting scientists after the promulgation of the 1978 NAAQS for lead. Furthermore, a measure of the amount of progress and scientific sophistication that has occurred in the lead field over the past 28 years since the last primary and secondary NAAQS for Pb in 1978 were promulgated can be readily discerned in considering how the 1978 standard was derived by staff of the OAQPS using the 1977 Pb AQCD. That methodology was based on a mix of empirical exposure data, health guidelines and ad hoc statistical relationships.

The all-important averaging time and form of the averaging was: a maximum arithmetic mean averaged over a calendar quarter. The original proposal in late 1977 was for an averaging time of 30 days, based on considerations of then-known blood lead toxicokinetics in children and adults [42 FR No. 240, 63076-63094, 12/12/77]. However, the final ruling entailed a selection of a calendar quarter [43 FR No. 194, 46246-46277, 10/5/78]. The shorter the averaging time and the more stringent the form, the less in the way of exceedence extent or frequency is permissible.

The chapter does a reasonable job of describing the construction of the models, their ability to deal with predictive modeling requirements in actual use, etc. The Chapter also does a good job of model comparison. However, I do not understand what the Agency is actually supposed to do with this modeling chapter. The Chapter offers descriptions and model anatomies, but there remains the question of what happens with whatever the review produces.

The historical models are not currently in use and are not likely to be used. The IEUBK model, one confined to childhood lead exposure risk assessment, is in routine use and has been the standard risk assessment tool of EPA for numerous risk assessment and risk management decisions at many Superfund sites.

The IEUBK model has been reviewed by two CASAC committees, in 1989 and 1991-92. I was one of the ad hoc advisory members of both of these committees. Those committees found the IEUBK model sound for use and they approved applications for use in communities with lead point sources and use at hazardous waste sites, such as Superfund sites. Since the findings of those committees, the IEUBK model has been heavily-evaluated as to source code validity and field applications. In fact, a whole EPA symposium in 1996 with a monograph (EHP, v. 106 Suppl. 6, December 1998) was given over to modeling of exposures, with a significant focus on

the IEUBK model. The IEUBK model has also been enshrined in numerous Agency policy decisions over the years, such as those issuing from OSWER.

There is arguably not a lot the present CASAC committee can or should do at this point regarding assessment of the IEUBK model beyond acknowledging the reasonably satisfactory performance of the IEUBK model in the field. Arguments have been made over the years for revising the model to make wider use of probabilistic rather than central-tendency deterministic values in the exposure module. A battery of probabilistic components obviously only works with a lot of hard data available, otherwise uncertainty reduction remains problematic. One cannot even begin to think about probabilistic modeling of each of the numerous biokinetic components in the biokinetic portion of the IEUBK model. At present, there is some provision for accommodating inter-child variability in the Pb-B output.

I don't believe at this time that the direct use of the O'Flaherty or Leggett models as stand alone entities are feasible operationally or computationally in terms of evaluation and validating for wide use in risk assessment of lead exposures. Neither is ready for prime time and these two models are currently little more than computational and conceptual templates for the All Ages Lead Model (AALM). The relative status of these two models as stand-alone systems has been addressed by the SAB AALM panel.

The SAB AALM panel was charged with evaluating the first full iteration of the AALM model and its associated manual. It was never presented with the question that is being presented to this panel of modeling reviewers: *If the AALM model is not ready to go, which extant models would serve for use until that model is user-ready?* Had the question been posed, I fully expect that the panel would have responded. Although some of the SAB AALM panel members are also on this CASAC committee, I'm not clear on how or why the present panel would be any better equipped to answer the charge questions than the AALM panel would have been.

Turning to the details of Chapter 4, Table 4.1 material does not match its text, on p. 4-13, 1st full par.

There appears to be some confusion about whether it is erythrocytes or whole blood that begin to show curvilinearity with lead uptake at a lead level of 15-20 μg/dl. The literature is clear on this point, as pointed out in the 1986 AQCD: Chapter 10. Whole blood lead is linear versus daily Pb uptake up to about 40-50 μg/dl whole blood (RBC level of 100 to 125 μg/dl, assuming a Hct of 40%). See the cites DeSilva, 1981; Manton and Cook, 1984; Marcus, 1985a,b,c in the 1986 document.

QE1. Have any important new animal toxicology studies been overlooked in Chapter 5?

The Chapter's sections on lead and experimental animal organs and systems seems to be reasonably complete in terms of the studies that have appeared since the 1986 AQCD for Pb. Generally, the same can be said for the in-vitro studies cited. I believe the question of completeness in data should be mainly reserved for the principal systems that show the most robust dose-toxic response relationships, since those are the systems that will principally figure in the eventual use of the data by the Agency in consideration of changes in the NAAQS: that is, the developmental neurotoxicological, the immunological, and reproduction and development.

Some of the Chapter 5 sections are relatively new compared to 1986, e.g., immunotoxicity, while others have had much of their basic toxicological data presented in 1986, e.g., the hematological effects.

One format change that would make it easier to sort out thoroughness of data gathering is to have a standardized way for presenting human, in-vitro and animal data. As it is now, there's a range of organizations that are quite confusing. In some cases, human and animal data are mixed within subsections. A second recommendation is to make use of as many tables as possible and discuss in text only the data most useful for highlighting.

The major studies that deal with multi-system toxicological mechanisms that are critical for understanding the toxicological phenomenology are well represented in the neurotoxicological, renal, cardiovascular, immunological and other sections.

QE1a. Discussions in the neurotoxicology section focus mainly on lead effects on...Are there other pertinent areas missing or not adequately covered?

One topic within toxicological mechanisms that could be included in the neurotoxicology section is the whole multi-organ/multi-system issue of oxidative stress as a potent injury mechanism in multiple organs and systems including the brain. For example, Vaziri and Ding (2001) showed significant decrease in NO availability in the brain, kidney, aorta and heart of rats. They also showed NOS was increased in cerebral cortex and brain stem. The anti-oxidant enzyme Cu, Zn-superoxide dismutase was significantly increased in brains of Pb-Treated rats (Vaziri et al., 2003).

QE1b. To what extent does the...literature provide evidence for developmental lead toxicity having a permanent impact on bone and teeth...and for these tissues serving as storage pools...

Beyond infancy and toddlerhood, when bone lead is less labile toxicokinetically, net bone formation with lead deposition occurs. We know from diverse data that in older children and in adults, bone lead is a major store whether we are speaking of non-occupational or occupational populations. Bone lead release occurs as a consequence of lead following, as Aub noted in 1925, "the calcium stream." It is not necessary that there be deranged mineral metabolism. Bone lead release can occur in quite young individuals with any history of lead exposure. For example, Markowitz and coworkers showed that immobilization of children during hospitalization produces significant elevations in Pb-B, concomitant with the expected demineralization of skeleton and lead resorption. Numerous studies now document releases of bone lead under physiological or life cycle conditions, such as those of Gulson et al. using stable Pb isotope mixing for study of pregnant and lactating subjects and the postmenopausal women with osteoporotic changes by Silbergeld et al., 1988.

Is lead osteotoxic as well? Does Pb osteotoxicity in turn affect bone's role in body lead storage? The former Q is clearly answerable in the affirmative, and in the case of experimental animal studies, there are long term effects from chronic lead exposures. But it is not clear what level of persistence or actual irreversibility of osteotoxic effects in humans occurs. One body of older data we have for lead-induced skeletal mineral derangement in humans are numerous

reports in the time of much higher lead exposures of the presence of "lead lines" in older children. These are not lead deposits, but are multiple banded areas of dense mineralization at the metaphyses of the growing long bones.

E1c. Are the animal studies with chelation agents relevant to studies in humans?

There is potential virtue in studying the use of chelating agents in animals in terms of relevance to humans, but there are some practical considerations. First, we know from the multi-center TLC studies of the use of Succimer as an intervention agent to attempt reversal of neurobehavioral deficits that Succimer intervention does not prevent (apparently irreversible) deficits (Rogan et al., 2001; Rosen and Mushak, 2001).

Different agents have different modes of action and it would be difficult to model lead exposure changes in the presence of chelant use.

E1e. Does the oxidative stress theory appear plausible for lead toxicity and represent a common mode of action across species and organs?

The oxidative stress theory is not only applicable to lead toxicological mechanisms but a number of the sections of Chapter 5 appropriately discuss the elements of injury from, e.g., ROS.

E1f. Concentrations of Pb compounds used in animal toxicology...often appear high...what advice can the panel give...to identify a cut off value...?

That's a peculiar Q, albeit an interesting one. First, doses for animal testings are high because one wishes to first characterize the presence of an overt effect at the high end of the substances's dose-response curve. This has been a dictum of toxicology for decades. One then creeps down the dose-response curve, in the case of noncarcinogens, until one hits LOAEL and NOAEL values, with or without enough data to generate Benchmark Dose values.

Second, different organs, systems, and species have different sensitivities to lead dose/exposure. It's not possible to readily answer the question because there's not a one-experimental-size-fits-all answer.

Thirdly, we have plenty of epidemiological data for human risk populations as extensively set forth in Chapter 6, so that it's not clear what we want at this stage of the field from animal data in terms of QUANTITATIVE DOSE-RESPONSE yardsticks as compared to QUALITATIVE MECHANISTIC INSIGHTS. The Lanphear et al. international pooling results show little evidence for a threshold in neurotoxic effects, especially those evaluated in that analysis. The association extends down to around the PRACTICAL QUANTITATIION LIMIT (PQL) of a reasonably good clinical laboratory, 1 μg/dl or so.

Fourth, there are potential inherent limitations to extrapolation of effects. In the case of inorganic As (As-i), for example, there are few good animal models for dermal and internal organ carcinogenesis in humans, even though we know As-i is a potent human carcinogen, with extremely low measured water levels of As-i associated with cancers (e.g., NAS, 1999 and 2001). Some have argued that the absence of a good animal model for various As-i effects raises doubts about its human toxicity. This ignores the obvious point that animal exposures are mainly

used as surrogates in the absence of data for human exposures and not vice-versa. What's more, EPA is usually in the business of using animal data to protect humans, and not vice versa.

Q F1. Does Chapter 6 adequately address the issue of dose/exposure metrics for use in human population studies?

Chapter 6 did a very good job of describing the pros and cons of using the various exposure biomarkers. I have already made comments elsewhere about the dose metric portion.

One point for further discussion, beyond the differences in using the various metrics, is their relative status in quantifying dose-response relationships. For example, Pb-B is the dose/exposure gold standard for dose-response relationships whatever its toxicokinetic and interpretive quirks.

What type of bone lead measurement does one do for bone lead-toxic response relationships? What level in which type of bone corresponds to a scaled series of toxic responses? The use of bone lead has to spread to beyond its use in a research setting. The VA Normative Study has produced a number of studies but the technique will require much more quantitative characterization and diversity of use to be accepted as a routine tool.

Q F2a. Does this Chapter adequately address questions regarding the significant neurotoxic effects observed at low blood Pb levels...Also, is the issue of model selection adequately discussed?

Yes, the Chapter adequately addresses a number of Qs regarding the lowest threshold for neurotoxic effects. The authors have presented several explanations for the overall curvilinear nature of the dose-response curve, with the lowest segment of Pb-B having the most comparatively robust effect.

Does the shape of this segment of the overall D-R curve reflect a more biased loading of misclassification of exposure into this lowest segment compared to higher Pb-b ranges?

On toxicokinetic grounds and the available literature on the temporal behavior of Pb-B in significantly exposed children, any explanation for the more robust lower segment is not readily forthcoming if the definition of misclassification is an erroneously assumed brain lead burden based on its surrogate, Pb-B. The lower the Pb-B, the lower the starting level of brain lead burden relative to brain Pb burdens in other children in the study with higher Pb-Bs, assuming that brain Pb half-life of clearance does not change with absolute levels in the tissue. That applies as well with cumulative lead burdens.

The lower the starting Pb burden in brain, for a given assumed half-life of decay, the more rapidly Pb-Brain reaches a potential sub-effect threshold value. Succop et al. (1987) reported that for the Cincinnati study cohort with quite elevated Pb-Bs in their earlier years of testing, i.e., > 10 μg/dl, the half-life of Pb-B was 10 months, compared to the more typical value for either low chronic or acute exposures of 20-30 days. The difficulty of ascribing this extended half-life to body lead burden is the inability in this and other cases to stratify the more persisting Pb-B elevations to endogenous or "washout" lead and simply ongoing elevated exogenous lead

intakes. If however, the half-life of lead clearance from brain is not independent of absolute Pb-brain level, e.g., dose-dependent induction of Pb nuclear inclusions, then things are even more complicated.

The question of model selection as a determinant is a biostatistical one, and I am not able to comment.

Q F2b. Does the summary section of Chapter 6 adequately and correctly reflect the content of the Chapter?

The answer is generally yes but some fleshing out of the summary would help. In fact, the language of summary is quite conservative, i.e., does not overreach. It is clear from this chapter and its reasonably correct reflection of the extant literature that lead injures multiple systems and does so through a multiplicity of mechanisms. Some of these mechanisms are insidious. This certainly characterizes those subtle effects that only become apparent when the organism is stressed in some way, whether it's an infectious episode, a mathematically complex test question at school, etc. More should be said about the need for test paradigms of lead neuroepidemiology and lead immunotoxicity to make sure challenges of the resting system are robust enough to see things start to fall apart.

Q F2c. There is concern as to what level of change for various endpoints constitute adverse effects. What are the Panel's thoughts?

The argument about what defines an adverse effect has very long legs. The matter has come up in every lead document preparation and review and every other consensus document that I have been involved with. There are various answers.

First, one can use the definitions set forth by the National Academy of Sciences back in 1977. In paraphrase, adversity of effect is defined by either some impairment of optimal function or reduction in reserve capacity to sustain optimal function. Note the operative term is optimal, not minimal. For all practical purposes, the definitions find themselves in the realm of low-level toxicity or sub-clinical effects in asymptomatic children.

Secondly, there is the matter of diagnostic and assessment tools to evaluate lead's toxic effects and the conclusions to be drawn from there. If one asked what is the principal adverse effect of lead in children in 1910, the answer would be "death" (Blackfan and Thomas, 1914). If one asked the Q in 1925, the answer would be "encephalopathy with coma and seizures" (McKhann, 1926). In the 1940s, the answer would be "recovery from acute poisoning but with severe cognitive and behavioral sequelae" (Byers and Lord, 1943). And so forth.

Thirdly, there is a societal dimension, i.e., societal expectation, to the definition. If one told a group of parents, at a meeting to discuss the hazards to their children of a lead operation next door, that their children would sustain a large drop in IQ but not enough to be considered clinical retardation, i.e., there's no problem, one can imagine the resulting response.

The notion of adverse effect also figures in the use of biomarkers of effect. European researchers and clinicians are much more cautious, on medical ethical grounds, that routine

biomarkers of effect be markers of earliest, biochemical effect without the biomarker being an index of an adverse effect. This has been due to the heavy influence of Lars Friberg and colleagues at Karolinska Institute, who produced a 1983 monograph on what are and what are not appropriate biomarkers.

Q F3. Are the discussions of genetic and other susceptibilities adequate?

They are generally adequate in that for cases of genetic susceptibility there are still Qs about what markers are in place to show such heightened sensitivity to lead. The ALAD allele population distribution case is telling. Elevated Pb-Bs in people with the ALAD 1:2 or 2:2 vs. the 1:1 variant may not mean more risk of toxicity but less. That is, what's significant is the tightness of Pb binding and removal from the vulnerable target organ pools until erythrocyte turnover occurs.

Mention should be made of the opposite direction in two phenomena: Pb-B is declining while the incidence and prevalence of childhood asthma is increasing. If lead is a factor, why is this? I believe that one matter that should not be overlooked is that those subsets of children with the highest increases in asthma rates are those whose numbers have been most refractory to Pb-B declines: inner-city, low-income minority children whose economic straits have been getting worse in the last number of years. Children forced into housing of ever worsening quality, for example, encounter more asthma risk factors.

Q G. Comments and suggestions for Chapter 7

It may be difficult for the panel to come up with a list for Chapter 7 until the review of the content chapters is finished. This may be something that could be discussed with a scheduled teleconference between Rounds 1 and 2. See, also, earlier comments about the synthesis sections in the previous AQCDs for Pb.

Q H. Does Chapter 8 cover the most relevant issues for environmental effects?

I have made a number of comments on 8 earlier in this pre-meeting review.

POST-MEETING COMMENTS – EPA PB AQCD

Reviewer: Paul Mushak, Ph.D.
March 6, 2006

I have a number of post-meeting comments. They cover both the assigned Chapter 4 and the remaining Chapters.

In addition to these post-meeting comments, I will be providing a short set of bullet lines for consideration for the letter to the Administrator.

Chapter 4 Comments

The panel's discussion of the models generally indicated that, for the foreseeable future, the IEUBK model is the one farthest along of the four non-historical models discussed. The All Ages Lead Model (AALM) is still early in development and has little near-term readiness for use in EPA health risk-based assessments of Superfund sites and other sites of concern. The AALM model is also currently being reviewed by a separate panel of the SAB. The O'Flaherty and the Leggett or Pounds Leggett PB-PK models as stand-alone Pb exposure predictive models still need work. This leaves the IEUBK model for the near term.

A number of panel discussions occurred about the desirability of modeling dust Pb as lead loadings, given that studies have shown that dust Pb as loading is a more robust predictor of dose for dose-response relationships than dust Pb as concentration. I would also note that even moderate levels of lead in air can produce a surprisingly large impact on lead exposure pathways. This occurs for the very young child via dust lead loadings onto interior hard surfaces and also Pb loadings onto exterior hard surfaces, e.g., toy surfaces, outside picnic tables, etc.

I have some comments about the issue of lead loadings and any subsequent use in modeling. It is important to note that in the present context we are speaking of dust lead loadings to hard surfaces contacted by children. Dust lead loading and loading rates can also be applicable to soils, but that intermediate medium is not directly at issue for the loading question in terms of dose robustness in dose-response relationships.

All three of the models at issue are constructed to have their biokinetic components crunch on Pb input, which presently is the product of Pb daily intakes multiplied by uptakes (absorption, bioavailability) summed across media. To anthropomorphize the models, they don't care what pre-biokinetic calculations in the exposure portion occur that eventually produce intakes of lead per unit time. Lead intakes from dusts for subsequent uptake and biokinetic disposition, for example, can theoretically take the form of intakes derived from Pb as a concentration term multiplied by intake mass or as a lead loading per unit area multiplied by one or more parameters that govern transfer of amounts of lead from a confined hard surface area to the mouths of children for subsequent ingestion.

None of the three more finished models are currently constructed with an actual way to handle dust or soil Pb loadings, i.e., Pb level-per-unit-area, as a means to compute eventual daily dust Pb intakes into children's blood. In the IEUBK exposure module, in particular, intakes of dust Pb are derived via concentrations x intake masses. How does one derive a Pb loading rate and then get from a hard surface Pb loading, or Pb loading rate, to a daily lead intake? There are calculations one can make in several stages.

EPA's 1996 Integrated Report for the three-city soil Pb abatement demonstration project, on p. 2-25, provides the specific and simple calculation (Eq. 2-3) for obtaining dust Pb loading rates per annum for an air Pb level of 0.1 $\mu g/m^3$ and a reasonable estimate of the deposition rate in this setting of 0.2 cm/sec. From this specific expression, one can obtain the daily dust Pb loading rates in the usual metric of m2 for any Pb-air value where the deposition rate would be reasonably valid:

1×10^{-7} µg Pb/cm^3 * 0.2 cm/sec * 3.15×10^7 sec/year = 0.6 µg Pb/cm^2 * year

U.S. EPA. 1996. Urban Soil Lead Demonstration Project. Volume I: EPA Integrated Report. Report No. EPA/600/P-30/001aF.

For a hard surface, the result is 6,000 µg/m^2/year, or 16 µg/m^2/day daily dust Pb loading rate for an air level of 0.1 units. In units of ft^2/day, for cumulative loading comparisons in the units of the EPA Lead Hazard Rule standard for floor loading, 40 µg/ft^2, this is 16.0/10.8 = 1.5 µg Pb/ft^2/day. The EPA dust lead loading standard is for interior floor surfaces. The standard relationship of outdoor to indoor air lead level is:

Pb-air, interior = Pb-air, exterior * 0.3

(see p. 2-28) U.S. EPA. 1994. Guidance Manual for the Integrated Exposure Uptake Model for Lead in Children. Report No. EPA 540-R-93-081).

U.S. EPA. 2001. Lead; Identification of dangerous levels of lead; Final rule: 40 CFR 745 [66 FR 1205-1240; January 5, 2001].

An interior floor dust loading rate requires a calculation for interior Pb-air when ambient outside Pb-air is X by simply multiplying X by 0.30

The attached Table 1 presents the daily Pb loading rate for interior and exterior hard surfaces as a function of Pb-air along with loadings for a sample time interval, 90 days. The dust Pb loadings over 90 days are quite significant. Table 2 provides the relationship of daily dust Pb loadings to the EPA floor dust lead loading standard with respect to time periods (days) required to reach the standard.

The current draft of the AALM model has, in its exposure module for dust Pb, the choice of using dust Pb as either concentration or loading. The model also has a parameter selection for "contact rate" as a function of child age if one selects the loading option. The contact rate as specifically derived for this model apparently links the loading per unit area to an ingestion total or rate by incorporating estimates of such physical and behavioral parameters as fractional transfer of surface Pb to hand per pass, as fractional transfer of hand Pb to the mouth via mouthing per event, and the frequency/day of these passes for a locale with the indicated surface Pb loading. This is surmised from the current draft of the AQCD, Chapter 4, on p. 4-31, which notes "...the lead ingestion rate being calculated as the product of loading and contact rate." In the actual AALM model, I found that this calculation in the exposure module appears to be disabled.

The contact rate in the AALM model differs with child's age, as would be expected. The drop-down dust alternative menu in the model is presented as Figure 22 in the AALM draft manual.

I would note that the question of transfers of contaminants from surfaces to mouths of young children has been of considerable interest to various agencies. For example, the Consumer

Product Safety Commission (CPSC) has developed protocols for testing Pb intakes from a combination of surface wipe data and Pb transfer to children's hands and subsequent ingestion. EPA's pesticide regulation program and the CPSC have also been looking at children's hand contact and transfer data for such exposure settings as contact with play products built from chromated copper arsenate (CCA)-treated wood.

The IEUBK model is only applicable to lead exposure modeling for children out to 84 months of age. It does, however, have the virtues of extensive evaluation and calibration and having a current routine risk assessment role for lead at such locales as communities impacted by Superfund sites. All 10 EPA Regions routinely use the model in their Superfund programs and have been doing so for over 10 years. A quick scan of completed Superfund action documents involving the model's uses can be done via the Regional web sites. They are numerous. I and a number of others, both on the Ch. 4 subgroup and other members, had considerable difficulty as to (1) what bodies of empirical data or combinations of empirical data and modeling approaches should weigh proportionately more significantly in the thinking of EPA with respect to addressing NAAQS review, and (2) how would the panel's time at the meeting and afterward be best used for this particular purpose.

One area of focus with respect to tandem use of modeling and epidemiological data should be the downstream step where distributions above and below a target Pb-B level would be determined so as to comply with a selected percentile protection cutoff. In the IEUBK model, the current Pb-B value to be avoided for 95% of affected children is 10 µg/dl. That is, EPA's current practice is to use a protection percentile, 95%, whereby remediation actions will be such that 95% of all children will be below the criterion value of 10 µg/dl.

The thrust of the current data is that the target Pb-B for applying the protection criterion should be well below this current level of 10 µg/dl.

The question of CDC views on sub- 10 µg/dl thresholds for effects and the relative feasibility of acting on those findings are noted for Ch. 6.

Consideration should also be given to the dust Pb impact, where the dust Pb loading is related to air Pb.

Other Ch. 4 Comments

Some specific concerns were expressed about Chapter 4. Dr. Cory-Slechta questioned the source of the half-life of lead in the brain being two years. That figure is from the Leggett, 1993 paper, which cites earlier data in experimental animals. I also found this half-life to be perhaps longer than expected. This matter of brain Pb $T_{1/2}$ is important because it may influence the interpretation of such outcomes as persisting effects, the most robust indicator of neurotoxic injury, etc.

One factor in assessing Pb levels and Pb changes in tissues over time and dosings is a methodological one. We found some years ago in our animal studies of lead distributions in tissues of rats and other animal models that tissue levels showed changes with perfusion of the

animals to avoid occluded blood. Blood of high Pb content retained in target tissues would affect both measured absolute levels as well as rates of change with changes in exposure.

Dr. Miller was concerned about the source of the pulmonary compartment deposition figure in the IEUBK model of 32% for children. The lung deposition figure of 32% is based on the data in the 1989 Staff Paper of EPA-OAQPS:

> U.S. EPA. 1989. Review of the National Ambient Air Quality Standards for Lead. Exposure Analysis Methodology and Validation. U.S. EPA Office of Air Quality Planning and Standards, Research Triangle Park, N.C. Report No. EPA-450/2-89/011.

That source noted child lung deposition of Pb as 25-45% for children living in non-point source areas and 42% for those living near point sources.

This document badly needs a section where the whole issue of bioavailability, i.e., uptakes from the receiving body compartments of both ecological and human risk populations can be presented. There is the expertise among the authors to do so. The topic is sprinkled throughout the document with little emphasis. Chapter 4 is the place to do it. The material is largely present, just scattered. I would especially urge that a section of Chapter 4 be given over to the various determinants of Pb bioavailability: biochemical, physico-chemical, anatomical, physiological, thermodynamic, etc.

> Mushak P. 1991. Gastrointestinal absorption of lead in children and adults: Overview of biological and biophysico-chemical aspects. Chem. Speciation Bioavail. 3: 87-104.

Comments on Other Chapters

Ch. 6

I like the notion of discussing further the distinction between the evidence of sub-10 μg/dl effects and the conundrum of what to do about these findings. CDC has had the problem in its most recent statements of saying there are low-level lead exposures that produce effects below 10 units in Pb-B, while simultaneously and passively holding that the reduction of such exposures is problematic. This is an odd approach for a health agency. CDC should simply and actively argue for primary prevention approaches to remediate low but still potent lead exposures.

Dr. Schwartz, in the quite appropriate mercantile vernacular, likened agencies using lead exposure data to marketers of data and actions of several types. CDC can be considered as a retailer and EPA as a wholesaler of not only health data but their disposition. This is critical to keep clear. I would note that we now have such low levels of lead exposures causing adverse effects, as evidenced in current studies, that what is required for intervention in hazard reduction are primary prevention modalities, not secondary ones.

> Rosen JF, Mushak P. 2001. Primary prevention of childhood lead poisoning: The only solution. N. Engl. J. Med. 344: 1470-1471 (editorial).

EPA, by statute, is a regulatory agency and therefore has the means to implement primary prevention modalities, i.e., it wholesales primary prevention to others. CDC, by charter, is a health advisory agency with no primary prevention powers and the burden of having to deal with secondary prevention realities. That is, CDC concerns itself with children already lead-exposed enough to have elevated Pb-Bs. Such children also are recognized by CDC as justifying primary prevention without having the authority to dictate primary prevention. EPA, along with the U.S. HUD, the U.S. FDA, and U.S. CPSC are empowered to implement primary prevention approaches to dealing with sub-10 μg/dl effects. Just because CDC has to rely on regulatory agencies to implement primary prevention approaches to reducing child lead exposures is no reason it cannot aggressively provide and push the rationales for primary prevention to such regulatory agencies as EPA to begin with.

Chapter 8

The section on amending soils with phosphate to immobilize Pb should be expanded to include a discussion of limits to phosphate amendments where lead co-occurs with arsenic (As) in contaminated soils. It is often the case that extractive industry emissions of lead to soils are accompanied by co-deposition of highly carcinogenic inorganic As (As-i). Aerated soils contain As-i as the pentavalent form, arsenate. Phosphate would mobilize arsenate through competitive binding, creating the risk of moving arsenic down into groundwater. As-i in drinking water is a particularly hazardous combination, in that As-i in water is a potent human carcinogen. See the 1999 and 2001 NAS/NRC reports on the topic.

Synthesizing Chapter

This chapter is where the massive amount of data in the draft chapters is winnowed down to those key aspects of the total data base in the previous chapters and the key data for further Agency analysis that are relevant for the low-level toxic effects and exposures associated with them are selected. The guidelines for doing the synthesis chapter spring from the various critical comments made by the panel members at the meeting.

First, the most holistic synthesis of the quantitative and qualitative realities of the current environmental compartmental lead inventories (in terms of multi-media exposures of children and other risk groups) should be done and made clear. That is, the extent of permissible further Pb inputs to human exposures must account for media-specific Pb accumulations.

The legislative history of the control of lead and other contaminants has typically made for piecemeal or media-specific controls. However, toxicology and biology integrate total intakes into a collective measure of overall risk.

Mushak P, Schroeder C. 1980. Multi-media Environmental Pollutants. A Report to the National Commission on Air Quality, Washington, D.C., December, 1980. Summarized in: To Breathe Clean Air, Report of the National Commission on Air Quality, Washington, D.C., March, 1981.

Schroeder C, Mushak P. 1980. The Legislative History of Multi-media Pollutants. A Report to the National Commission on Air Quality. Washington, D.C. December, 1980. Summarized in: To Breathe Clean Air, Report of the National Commission on Air Quality, Washington, D.C. March, 1981.

Then, the most reliable data from mechanistic, experimental and epidemiological studies that define the lowest levels of Pb-B associated with adverse effects should be retained for further assessment. This should be made easier by using chapter-specific Executive Summaries.

Some summary statements should be used to wrap up the rest of the studies.

Again, the synthesis chapter should be placed after the environmental effects material, and include summary analysis of those effects. The recommendation for use of both document-wide and chapter-specific Executive Summaries is a good one and should be adopted. Policy wonks and the generally interested public typically read only the ExSums. If the essence of the effort is not there, it will go unrecognized.

TABLE 1. Relationship of Ambient Air Pb to Dust Pb Loading and Loading Rates*

Outdoor Air Pb ($\mu g/m^3$)	Interior Air Pb ($\mu g/m^3$)	Outdoor Dust Pb Loading Rate ($\mu g/m^2/d$)	Indoor Dust Lead Loading Rate ($\mu g/m^2/d$)	Outdoor 90-Day Pb Loading ($\mu g/m^2$)	Indoor 90-Day Pb Loading ($\mu g/m^2$)
0.10	0.03	16.0	4.8	1,440	432
0.25	0.08	40.0	12.0	3,600	1,080
0.50	0.15	80.0	24.0	7,200	2,160
0.75	0.23	120.0	36.0	10,800	3,240
1.00	0.30	160.0	48.0	14,400	4,320
1.25	0.38	200.0	60.0	18,000	5,400
1.50	0.45	240.0	72.0	21,600	6,480

* Calculations based on EPA 1996 and EPA 1994.

TABLE 2. Relationship of Ambient Air Pb to Dust Pb Loading, Loading Rates, and the EPA Lead Hazard Rule for Interior Dust Pb*

Outdoor Air ($\mu g/m^3$)	Indoor Air ($\mu g/m^3$)	Indoor Dust Pb Loading Rate		Days To Reach 40 μg Pb/ft^2 **
		$\mu g/m^2/d$	$\mu g/ft^2/d$	
0.10	0.03	4.8	0.44	100
0.25	0.08	12.0	1.11	36
0.50	0.15	24.0	2.20	18
0.75	0.23	36.0	3.33	12
1.00	0.30	48.0	4.44	9
1.25	0.38	60.0	5.55	7
1.50	0.45	72.0	6.60	6

* Calculations based on EPA 1996 and EPA 1994.

** EPA floor dust Pb standard: 40 CFR 745.

ADDITONAL POST-MEETING COMMENTS – EPA PB AQCD

Reviewer: Paul Mushak, Ph.D.
March 9, 2006

Additional Chapter 4 Comments

[CASAC Lead Review Panel Member] Fred [Miller]'s e-mail and my original comments need to be juxtaposed in a common context. The context is simply the scientific interplay of models and empirical data vis-à-vis the AQCD draft and its required connection to evaluation of the primary and secondary NAAQS. We are not at all concerned in this chapter whether someone can get either the ACSL or the C++ Basic Desktop versions of the O'Flaherty model to do a simulation of a Pb-B. In fact,… I've used the desktop version of O'Flaherty to make runs over the years. I'm not averse to use of O'Flaherty. The problem is broader than this.

The modeling chapter cannot escape its linkage to risk assessment use for population assessment, whether that assessment is for air regulations or some other purpose. The O'Flaherty model still needs more evaluations with field data; the O'Flaherty model, to the best of my knowledge still needs a discrete exposure model for handling batch runs; and the O'Flaherty model needs a statistical module for descriptive and inferential statistics. Cutting to the chase, when I say a model is ready to go, I don't mean someone can run it for a single output in Pb-B, but rather that it can handle the risk assessment needs for lead-impacted groups, however large or small they may be.

Secondly, we're also in a pickle, as I noted in my pre-meeting comments, about harmonizing what this sub-group is saying about the modeling issues versus what the SAB [*Ad Hoc* All-Ages Lead Model] AALM [Review] Panel (all of whose members were focused only on modeling), have to say about modeling and the models. As [CASAC DFO] Fred [Butterfield] can attest, there are a number of places in the comments and reportage in the AALM panel's report now being finalized about not only the AALM model, but the O'Flaherty, Leggett (Pounds Leggett) and IEUBK models. Seeking consensus among us four sub-group members would probably be relatively less turbulent than the U.S. EPA having two parallel advisory panels having divergent things to say about the same topic.

Secondly, there is the use of slope factors versus modeling. Again, the role of regression analysis-derived slope factors is in the context of utility for subsequent usefulness for risk assessment of lead-impacted groups. The panel was not convened to apply a slope factor to a single community or a discrete study.

In the [February 28-March 1, 2006 CASAC Lead Review Panel] meetings, my recollection is that [CASAC Lead Review Panel Member] Bruce Lanphear was not arguing in any adversarial way for slope factors to be the choice rather than modeling. He mainly had questions about modeling per se. They are not the same thing. [Panel Member] Joel Schwartz pursued at more length the use of slope factors. Now, consider what is being said. What's being said is that one can presumably take some central tendency expression of the slopes from 12 pooled studies, some in inner urban and some in isolated mining/milling/smelting communities and come up with a slope factor that can be applied anywhere else that EPA wishes to use this value. Consider using this slope factor versus using a model, any model, that permits discrete inputs to the exposure module from each and every of the multitude of specific sites where an air lead, say, is measurable via either primary emissions or fugitive dusts. No one is proposing using any of the models to come up with a national Pb-B based on single national snapshots of environmental lead inputs. But one presumably would be proposing using the slope factor equivalent if this approach were employed.

There is also the problematic nature of Pb-B measurement. A number of the studies contributing data to the pooled study at issue for dust/soil Pb versus Pb-B were "single shot" Pb-B measurements. Consider that a significant point being made in Chapter 6 and elsewhere in the draft AQCD for Pb is that single-shot lead measurements are highly limited (unless, of course, one wants to use the single measurements for deriving slope factors). The matter drips with inconsistency.

The 12 or so pooled studies of dust/soil vs. Pb-B, keep in mind, are centered on children. These pooled studies drew on existing studies that were based on kids, not the entire range of ages. So, no particular disadvantage attaches to models limited to kids when slope factors would be limited to kids.

Alternatively, if one proposes to do an ad-hoc study using measured Pb in various media and measured Pb-B for each and every site to come up with a specific slope factor where a model might be used, one then has the problem of single-shot Pb-B measurements and more overall resource costs.

Finally, I would note that the model vs. ad-hoc slope factor issue is, to quote Yogi Berra, "déjà vu all over again." Slope factors were the first approach, many years ago, but this strategy had so many problems in terms of broader relevance, that mechanistic models were developed. My collective sensibility after 38 years in the lead and other toxic metal field is taken aback by some having us regress back to regressions.

[Note: Excerpted from Dr. Paul Mushak's e-mail message sent 03/09/2006 at 02:36 PM]

Dr. Michael Newman

Dr. Michael Newman
Virginia Institute of Marine Science
February 28, 2006

In general, Chapter 8 appears to be well written and comprehensive. The authors should be complimented for their efforts. In the spirit of enhancing their work, I offer the comments below. Many of them may reflect personal opinion but are offered just in case they help.

The figures in the manuscript are clean but often what exactly is being plotted or communicated is not straightforward. This makes some figures difficult to grasp without effort, e.g. what exactly is the x-axis of Figure 8-1.5.1 or 8-1.5.2? Is it cumulative proportion of ranked values? If so, the scatter in the plot is confusing.

Page 8-76
The rationale behind using the highest bounded NOEL that was lower than the lowest bounded LOEL for survival, growth and reproduction for the TRV is difficult to understand as the paragraph is currently written. Although it is important to be balanced about providing too much detail for the many issues discussed in the manuscript, I would ask that the authors please provide more justification. This is particularly key in my mind as the TRV and bioavailability estimates are so important.

Page 8-81, lines 50-51.
The statement is made that growth and reproduction were considered because they are the most ecologically relevant [compared to biochemical, physiological, pathological or survival]. I do not understand exactly what is meant as the other factors certainly do influence the ecology of an organism. The most obvious is survival: a dead organism certainly has a different ecology than a living one. Behavior is relevant to fitness within a community so it is also ecologically relevant.

Page 8-91, lines 1-11 of text describe the selection of study results based on consistency with the overall set of results. Because the observation of "significant" effect is usually made in each paper with a statistical test, it is odd that this discussion does not include any consideration of design/test power. If one test shows an effect in contrast to many that do not, that does not mean it should be disregarded. It may be that that study was the most powerful one. I would ask that some consideration of power differences due to design and testing issues be included in such selection of studies for use.

Page 8-91. LC50 values are reported with estimates of uncertainty. It is customary to use 95% fiducial (confidence) intervals but these values seem to be presented as one would a standard deviation or standard error. Which is being expressed here?

Page 8-98. The transition is made from considering effects to individuals to those to ecosystems without any separate discussion of population or community level effects. This is confusing to me because EPA states in numerous documents that protection of population persistence/ viability within natural communities is their intent when assessing ecological risk. As the

manuscript stands, the effects are discussed as either to individuals or to other all other levels of ecological organization. I would prefer to see separate discussions of population, community, and ecosystem effects because they are equally important. Combining them as done here makes it too easy to not mention an important effect at one of these levels. (This blending of population, community, and ecosystem effects into "ecosystem" effects after discussion of effects to individuals is done again on page 8-127.)

Page 8-117/118
The AVS/SEM approach described here is sound within the limits of the discussion. For organisms that can be exposed via particulate ingestion, it can be insufficient. This has been documented in several publications, including those by Luoma.

Page 8-130
This is an accurate description but the EPA method has shortcomings that should be discussed more relative to the purpose of this document. For example, it is biased toward metrics of effects to individuals and the associated calculations do not consider crucial ecological interactions, keystone species, or critical roles. Also, the selection of 5% is somewhat arbitrary.

Page 8-132
The FIAM is discussed as distinct – a "conceptual" model – from the BLM, and perhaps not sufficient as a consequence. This distinction should not be made because the BLM is also a conceptual model, i.e., it is not a physical model. The FIAM is a computational model when applied with a speciation computer program as is the BLM. I find the distinction being made unconvincing. It seems to push the BLM into the spotlight awkwardly. I suggest that the FIAM and BLM be discussed as models emerging from the same general vantage and then just discuss the details using the BLM. The discussion on page 8-167 seems balanced in this way.

Page 8-133, line 13-17
The movement of free ions through cell membranes seems to be presented immediately before suffocation and disruption of ion regulation in a causal sequence here. There are too many steps in between membrane transport and these consequences, such as oxidative damage, epithelial layer lifting, inflammation, excess mucus production/sloughing, and chloride cell changes, for this sentence to accurately represent the process. Please reword.

The discussion of the BLM having the advantage of using the "biotic ligand" instead of the gill to allow one to model the site of action in direct contact with the water does not seem clear to me. The gills are in direct contact with the water. The "biotic ligand" is a conceptual tool that likely is – but is not necessarily – in contact with water.

Page 8-134
The AVS/SEM approach is likely a good one for a metal such as lead, but may not be as appropriate for other metals with less "b metal" natures. The AVS/SEM depends heavily on an interstitial water exposure route and does not fully include uptake from ingested solids. A qualifying sentence might be good here.

Page 8-146
The preponderance of <DL observations was appropriately handled by focusing on the high samples; however, the specific methods by which this was done are unclear. Was a specific statistic used to examine the spatial distribution of these highest values? Picking one particular percentile (without an estimate of uncertainty) would seem prone to error. (Please see page 8-215 as an example where enough details on the statistical methods were provided.)

Page 8-154 (and elsewhere as appropriate)
Please describe and justify how means were calculated for censored data sets. Statements are made about concentrations being higher or lower than those for other areas but the associated statistical tests are not provided. The footnote states that censoring made definitive statements difficult. If one can't make a defensible statement using clearly defined methods then statements might be better left unsaid. If censoring is the issue, there are ways of estimating univariate statistics and testing for differences. (Please see Helsel, D.R., 2005, Nondetects and Data Analysis. John Wiley & Sons for the most recent compilation of associated approaches.)

Page 8-228 and onward
The discussion of critical load is very clear, providing a good understanding of the process.

Mr. Rich Poirot

Review Comments on 1st Draft Lead Criteria Document, R. Poirot, 3/7/06

I found Chapter 8 to be generally well organized and clearly written. The proposed approach to use the summary sections on terrestrial effects (8.1.1) and aquatic effects (8.2.1) as the main body of the chapter, with more detailed information intended to be appended as annexes, should improve the readability. The brief summarization of "pre-1986 knowledge" followed by more detailed focus of "new results" was effective. Some of the "conclusions" sections in the more detailed "annexes" were clearer and crisper than what was provided in the summary sections, and some of that language might be used in the new main body of the chapter in the next draft.

One general suggestion is to consider conducting the proposed "Integrative Synthesis" chapter after, and to include some information from, the Environmental effects chapter. I think this might be especially warranted for Pb, given the multimedia nature of lead exposures and the large historical burden of Pb distributed to many compartments of the environment (i.e. current human exposures are partly a function of what's been stored in or is being released from the environment). Since there is a strong tendency (or at least a tradition) of avoiding real consideration of secondary standards (typically and simply set equal to primary standards), an important set of questions that might be included in such a synthesis is whether there are environmental effects that occur at lead concentrations lower than, or for indicators, forms, or averaging times different from, those which effect human health.

There were several potential applications such as use of the Biotic Ligand Model (BLM) and the development of Critical Loads (CL) for lead deposition that appear to be promising ways to more carefully consider environmental effects and pollutant limits in the future, but which might not be quite ready for use at the current time. Staff can be commended for this eye toward the future, even as some caution is encouraged to assure that various bugs are worked out of these relatively new approaches. The critical loads approach – in relatively widespread use in Europe and Canada – seems like an especially appropriate approach for considering environmental impacts of pollutants like Pb, for which effects are more related to long-term cumulative deposition than to current ambient air concentrations. However, the caution on page 8-239 (that neglect of a factor for Pb transfer from the terrestrial catchment could result in a 5-fold underestimate of Pb concentration in aquatic systems) indicates that a CL approach for aquatic ecosystems needs to be further refined.

A conceptual question that might be raised in considering critical loads for lead or other pollutants is whether a secondary standard based on such CL calculations should most logically be expressed in units of deposition, or whether some approximate "conversion factor" could relate assumed deposition rates to measured ambient air concentrations. Most of the Chapter 8 discussion on environmental Pb measurement methods (8.1.2.1 – 8.2.1.6 and 8.2.2.2 – 8.2.2.6) focuses on analytical methods. This is useful information, but there could and should be better coordination with, and to the extent possible better linkages to (Chapter 2) methods used to measure Pb in the ambient air, precipitation, or dry deposition. At some point a direct linkage needs to be drawn between the many various effects of lead in the environment and the relative contributions to those effects from lead currently present in or deposited through the ambient air.

It's not a topic specific to the environmental effects chapter, but I think more discussion of particle size distributions in relation to environmental deposition and to ambient air sampling methods is needed somewhere. This may be of increasing importance if relatively coarse re-suspended roadside dust represents an increasing fraction of airborne Pb emissions. The FRM for atmospheric lead (atomic absorption on high volume TSP samples, with fiberglass filters) is not much in use any more, in part because ambient concentrations are typically so far below standards, but also because the relatively "dirty" and fibrous glass filters (with high and variable blank values for many elements) are not well suited for multi-pollutant analysis, and especially by inexpensive surface beam techniques like XRF or PIXE. There is a general movement in "air toxics" sampling programs to use PM-10 samplers. Meanwhile, fine particle Pb measurements by XRF on Teflon filters are relatively abundant in both urban (STN) and rural (IMPROVE) networks. If a revised secondary (or primary) standard were considered for Pb, how should it be measured?

It was interesting to note the substantial discussion - in chapter 8 and elsewhere throughout the document - of the potentially large emissions and environmental contamination of Pb (typically in association with, and with effects often difficult to distinguish from, other injurious metals like As, Cd, Cu, Zn) from various mining activities. A quick word search indicates about 170 instances of the words "mine", "mines" or "mining" in the Pb CD. Atmospheric emissions from such mining activities would tend to be primarily coarse mode particles, characterized by relatively high concentrations of multiple toxic metals. Yet such mining industry emissions are specifically exempted from consideration in EPA's recently proposed $PM_{10-2.5}$ standards. Some additional explanation for this apparent substantial inconsistency seems warranted.

Specific comments on Chapter 8:

8-3, line 24: "RBA" needs to be defined.

8-12, line 30: Can we have some additional information on the "three different soils" that might account for such a wide range (0 to 52%) of decrease in nitrogen reductase activity?

8-14 through 8-30: Generally it would be useful to better relate some of the analytical methods commonly employed for analyzing Pb in different environmental compartments vs. Pb in the ambient air. (i.e., better linkage to chapters 2 & 3). Also for methods like ICP-MS requiring sample extraction, are there any issues with extraction efficiency.

8-15, line 11: should be "factor … is" or "factors… are"

8-24, Figure 8-1.2.5: What is the shaded rectangle in this figure?

8-46, line 22: This "dry deposition may account for anywhere between 10 to 40% of total" is the only estimate of dry deposition I found (in this chapter), is a rather wide range, and is quite dated (1982). This also contrasts with other estimates provided in Chapter 2 (page 2-52). I would expect that the substantial source controls have likely reduced (fine particle and) wet deposition of Pb proportionately more than coarse particle Pb (since re-suspended roadside dust now

accounts for a high fraction of atmospheric Pb emissions). So likely the dry/wet deposition ratio has increased since 1982.

8-55, line 27: It might be informative to plot equations 8-1, 8-2 & 8-3 on a single graph – to illustrate log:log relationships of different biota to soil Pb.

8-146, line 19: Its unfortunate that the only surface water quality data you present has such a high frequency of non-detects. Are there no other useful data?

8-150, Figure 8-2.3.6 is not very clear.

8-157, line 2 and several preceding figures & pages: There seems to be a fairly consistent pattern of general Pb increases from West to East, but with several notable Western "hotspots". Can you provide any explanation for the cause of the hotspots?

8-239, line 1: should the CL units be mg/m2 (rather than mg/m3)?

Specific Comments on Chapter 2:

2-11, line 27: Over what spatial domain were these 19,000 tons emitted? Does not agree with the 12,000 tons in Table 2-6?

2-15, lines 11 & 16: These specific reported fractions of total US Pb emissions from primary & secondary smelters provide useful information, but do not seem to be reported in a similar way for other subsequently discussed source categories.

2-21, line 8: Not clear what "6.1% of all Pb in the United States" really means?

2-26, line 29: I assume you mean that the emission rate per liter of fuel is 50-100 times higher and not that total Pb emissions from waste oil are this much greater?

2-41, line 6: I think you mean "smaller than 2.5 microns" and not "smaller than $PM_{2.5}$".

Dr. Michael Rabinowitz

Comments on Chapter 3 of the First Draft By Michael Rabinowitz [02/23/2006]

Section 3.1 Air

This section on indoor air lead includes a lot of information about dust lead. Might the document be more usefully organized if dust and air were treated in separate sections? Dust particle sizes of 50 to 75 micron as an upper limit may not be respirable, but may well find there way into to digestive tract for absorbtion there (page 3-1 line 10).

Also on page 3-1, on the subject of removal of old lead paint perhaps add the following example. In the course of following a cohort of over 200 Boston children, it was found that about 68 percent of the households reported some sanding, scrapping, or other indoor surface refinishing at their residence in the previous six months, and in 34 percent of the homes there was significant levels of lead paint (more than 1.5 mg/sq cm) on at least one surface. There was an increase of 1.4 (SE 0.7) µg/dl in the child's blood lead among those where there was refinishing activity, compared to no activity. Furthermore, with increasing amounts of paint lead in the house, there was a larger increment of blood lead: 1.1 (SE 1.4, when lead paint was < 1/2 % by dry weight) to 2.8 (SE 2.3) for paint lead levels of 1/2 to 3%, and to 4.8 µg/dl (SE 2.2) when paint lead over 3% was detected, a 70% rise in blood lead levels. This demonstrates that household refinishing activity in the presence of lead paint can significantly raise the child's blood lead, at least temporarily (Rabinowitz et al.,1985b). (Could also be placed on page 3-33 line 18)

On the subject of indoor dust lead, it might be worth mentioning the strong correlations among indoor dust, indoor air and outdoor soil lead levels. For example, in Boston in a study of the homes of 248 young children, the Spearman correlation between indoor air and floor dust was 0.22 ($p<.001$), air and soil 0.18 ($p<.01$), and between dust and soil 0..43 ($p<.0001$) (Rabinowitz et al. 1985a). Similar patterns of correlations have been reported in Cincinnati and elsewhere. (Perhaps page 3-2, line 9 might be a good place to put this)

Section 3.2 Soil and Road Dust

On the subject of the response time of soil lead (page 3-13), two items might be added. Soil lead levels have been found to decline not only from "removal," strictly speaking, but also from mechanical mixing of surface soil with lower, less contaminated soils by the action of earthworms, tilling, and landscaping. This results in a dilution of the soil lead. This intentional landscaping by human activity is continually reshaped many urban and sub-urban environments. (Page 3-13, middle of page)

Despite this, soils from lead smelter sites have demonstrated the remarkable persistence of elevated soil lead, many decades after the suspension of industrial activity, particularly where the land has been left unused. For example Rabinowitz (2005) surveyed soil lead in the vicinity of old industrial sites to examine how the stable isotope patterns vary among the sites according to the sources of the lead ore processed at each site. Lead smelters and refineries, which closed down decades ago, are the basis of this investigation. Samples were taken from near five old factory sites in Collinsville and Alton (Illinois), Ponderay (Idaho), East Chicago (Indiana) and

Omaha (Nebraska). At every site visited, remnants of the old factories, in terms of soil lead pollution, could be found. (Maybe place page 3-18, line 9 or 10)

Page 3-18 soil lead near smelter- perhaps add:
Many old lead smelters go unrecognized, particularly secondary, battery recycling smelters. The current residents may not know that smelters operated in their area. For example, Eckel et al. (2001) identified approximately 430 defunct smelter sites in the United States by examining city registers and telephone directories from many decades ago. That compiled list was compared with government registries of known hazardous sites. Soil samples were taken from 10 sites. Only 5 of 319 sites, chosen from the top 8 states, were known to authorities. Nine of the 10 sites sampled exceeded residential standards for soil lead level. So, the location of most old smelter sites may be unknown to current inhabitants.

Section 3.4 Food
It may be of historic interest to note (perhaps on page 3-18) that food lead levels were significantly higher during the 1960's and early 1970s. Values of well over 100 µg/day in composite diets were found. Values in canned goods were exceptionally high because the packaging methods of that era consited of three part steel cans with soldered seems. These seams were soldered with a brush application of molten solder which introduced microscopic particles of "solder-splash" into the food. These methods have been superseded with welded and aluminum cans as well as other food packaging technologies. A recent Canadian Food Inspection Agency report bears on this matter:
(http://www.inspection.gc.ca/english/anima/fispoi/manman/canboi/ch7sec3/num15e.shtml)

Do you want to mention the occasional instances of intentional unscrupulous adulteration of food items with lead to increase the weight. Occasionaly batches of paprika are reported laced with red lead (J Toxicol Clin Toxicol. 1996;34(5):507-11). Lead intoxication epidemic caused by ingestion of contaminated ground paprika. Kakosy T, Hudak A, Naray M. From the National Institute of Occupational Health, Budapest, Hungary, for example. And another example from Germany (Dtsch Med Wochenschr. 1994 Dec 16;119(50):1756). [Lead poisoning caused by red lead in paprika powder] [Article in German] Lohmoller G.

Section 3.5 Other Routes

Section 3.5.3
Glazes perhaps add: Lead glazes are a particular problem when low temperature fluxes and glazes are used. This is often the case, for example, when traditional charcoal kilns are used, rather than gas fired kilns. Tea cups and dishes from the People's Republic of China, sold in the United States, supposedly only for decorative uses, frequently is in violation of the lead standards.

Section 3.5.6 page 3-34
Indeed some folk remedies intentionally contain lead. The toxicity of the lead may be responsible for the intended potency of the product. For example, such lead-containing products include alarcon, alkohl, azarcon, bali goli, coral, gliasard, greta, kohl, liga, pay-loo-ah, rueda and surma. These are of Mexican and Latin American, Middle Eastern, and Indian origins.

(Morbidity and Mortality Weekly Report 1999;48:27-29.) The lead content of these products can be more than fifty percent by weight. In other cases, lead is an unintentional contaminant, for example ayurvedic metal-mineral tonics, a fertility drug called Deshi Dewa, and a Chinese clamshell powder known as hai gen fen, which is a calcium supplement.

Section 3.6 Measurement Methods

It may be worth mention 2 points here. Firstly, the lead levels reported in this section range from percents (parts per hundred) to parts per billion. Consequently, concerns about contamination of the sample during sample collection and laboratory analysis vary greatly. Special care needs to be exercised when the same laboratory process samples across a wide range of lead concentrations.

Secondly, lead levels in food are often to low, that levels are below detection limits, and reported values are inferred rather than measured. Care must be exercised when these low levels are extrapolated back up to daily intake numbers.

Section 3.7 Summary

Perhaps add here of in the section on measurement something about bioavailability: The lead concentrations discussed here are usually total lead content, or lead measured by strong acid extraction. Although this does yield values for lead concentrations, it may not be the most useful approach. For the lead to be toxic it must be absorbed, and to be absorbed it must be bioavailable, or soluble in physiological fluids. In some situations, such as waste smelter slag this might be only a small fraction, while for tap water, it might be essentially all the lead. For that reason, care must be exercised in co-paring lead levels among the various rotes of exposure.

Additional Citations

Eckel W, Rabinowitz M, Foster G (2001) Discovering unrecognized lead smelting sites by historical methods. Amer J Public Health.91:625-7.

Rabinowitz M, Leviton A, Needleman H, Bellinger D, Waternaux C. (1985a) Environmental correlates of infant blood lead levels. Environmental Research 38: 96-107.

Rabinowitz M, Leviton A and Bellinger D (l985b) Residential refinishing and elevated infant blood lead levels. American Journal of Public Health 75:403-4.

Rabinowitz M (2005) Lead Isotopes in Soils near Five Historic American Lead Smelters and Refineries. Science of the Total Environment; 346: 138-148.

Additional Comments on the 1st Draft Lead AQCD by Michael Rabinowitz, Ph.D. [4/11/2006]

I had offered some suggestions at the time of our meeting, mostly about chemical forms and sources of environmental level lead.

Also, I want to express my concern that the issue of confounding of lead's effects on child development, as they appear in the section on the epidemiology of lead's impact on human health are not fully developed or adequately explored.

Unlike most other environmental pollutants, lead's effects, as we encounter them, are strongly confounded by other risk factors. The extent of this confounding varies among the populations studied, depending on the patterns of lead exposure in the particular circumstances. For example, is lead exposure correlated or not with social class or family income.

It is worth remembering that lead's effects are small, only a few IQ points, typically, compared to other much stronger determinants, such as parental education or family income. This is especially true at the lower blood lead levels currently being explored, now typically below 10 µg/dL.

For me, this is especially potentially troublesome because lead is usually considered as a continuous variable, well measured, while often the other variables may be expressed as categorical variables, so small differences in these factors, when lumped into the same category, cause differences in the outcome which could be ascribed to lead. For example, if the mother graduated only 8th grade or 9th or 10th, they could all be scored as not graduating high school. I do hope my concern about this is unfounded, and closer examination will show me worried needlessly.

As I tried to explain, I think these circumstances require us to look at each of the studies to examine the extent of the confounding. For example, in a given study, the model predicting IQ as an outcome, can be made with and without a lead term; and then seeing if adding the lead term (and the additional degree of freedom) statistically-significantly improves the model's goodness of fit. This would tell us if lead is an independent risk factor. Also, examining the effect of adding the lead term on the regression coefficients of the other terms would tell us in a quantitative way the extent of the confounding in that population. For example, does the coefficient for parental education change significantly when the lead term is added. In this way we can see how free the lead effect is from confounding, and hence how reliably the lead effect was measured in that study. This would enable us to put more weight on studies where lead's effects were more cleanly measured.

These concerns, and the suggested approach to addressing them, can be developed more as the human epidemiology synthesis chapter is reviewed.

Dr. Joel Schwartz

Comments of Joel Schwartz

In general, I like approach of interpreting epidemiology in the light of toxicology. It is important to cross-connect between these results to interpret the data in its entirety.

We need to be careful in the discussion of measurement error in **outcomes**, and the implication of such error. Assume that the outcome is normally distributed, like cognitive function. Then in a linear regression with a set of p covariates, and n observations, the predictors of the outcome are an nxp matrix, which is conventionally denoted X. Let the true outcome be y (an nx1 matrix). Assume that y is mis-measured, and we instead observe Z, with

$$Z=y+u$$

And u is random measurement error. Then recall that in a linear regression the vector of regression coefficients is estimated as

$$\hat{\beta} = (X'X)^{-1}X'Z$$
$$= (X'X)^{-1}X'y + (X'X)^{-1}X'u$$

Assuming that the measurement error in outcome is uncorrelated with exposure the last term has expectation zero. Hence, measurement error in the outcome induces NO BIAS in the estimate of effect of lead, unless e.g. the error in assessing blood pressure is correlated with lead exposure. Now consider the precision of the estimate. In a linear regression, we have

$$Var(\hat{\beta}) = (X'X)^{-1}Var(Z)$$
$$= (X'X)^{-1}Var(y) + (X'X)^{-1}Var(u)$$

Since the last term in this case has a positive expectation, the standard error of $\hat{\beta}$ will be biased upward. Hence the implication of measurement error in the outcome, except in the unlikely case that it is correlated with lead, is to reduce the power to detect a significant effect, but not to produce any bias in the estimate of effect.

P. 6.4 There is some leftover language from the PM document still in here. For example, the discussion of whether the exposure marker reflects the geographic differences in exposure seems PM-related. Presumably, we are asking whether it reflects the interpersonal differences in exposure, for a specific averaging time.

Pp. 6.6-6.7 Emphasis should not rest on studies combining results in different cities, this seems left over from the PM document. For lead, the issue is studies reporting combined results for different cohorts, or, more generally, different study populations. In general replace the phrase multi-city study everywhere it appears. Again, meta-analyses are of different study populations, not “various cities.” Similarly for the discussion of heterogeneity.

P. 6.14 The conclusion that a single blood lead can be expected to be a relatively poor index of body lead is too broad. It is derived from the simulation where there was a sudden, large, and temporary change in blood lead levels due to a sudden, large, temporary change in lead intake. In other circumstances, it may do much better. Also, remember, in a regression analysis it is the variation in exposure across subjects that is correlated with the variation in outcome. So, as long as the blood lead accurately reflects the relative ranking of subjects, all is not lost.

P. 6.14 Be clear that a better measure of the long term lead body burden is not necessarily what is wanted for an epidemiologic study. If the effects of lead on a particular outcome are lasting and cumulative, it is the preferred measure. If the effects of lead on the outcome represent the acute effects of current exposure, than long term body burden is not the preferred exposure metric. In the absence of clear evidence from toxicology as to which averaging time is most relevant to a particular outcome, we must look at both.

P. 6.22 needs to make clear in the discussion of "methodological" vs. "epidemiologic" methods for dealing with "detection limits" that:

a) The use of the phrase detection limit is somewhat misleading. We are really talking about measurement error. The instrument detects values less than 3 SD of background or measurement error. The values are merely quite imprecise. This is measurement error. On average, values of e.g. 1SD above background are truly less than values of 2 SD above background, although both are "less than the detection limit". Hence the real issue is measurement error.

b) To assign values below the "detection limit" a value of, for example, half the "detection limit" results in biased estimates of the association of bone lead with outcome. Assigning the measured values, even when negative, does not lead to biased estimates of the slope of the association of bone lead with outcome.

Pp. 6.28-29 The sentence "In contrast to using urine as a proxy for serum and measuring lead isotopes … " needs to be rewritten to clarify what Gulson did that was different, and better.

P. 6.40 Again, the discussion here seems to assume a priori that we want to measure body burden, and all biomarkers of lead exposure, in this case urine lead, are discussed in the context of how well they perform as surrogates for body burden. However, this is not the case. Lead can have immediate effects. For example, it is lead concentrations in plasma, and not body burden (except to the extent it provides endogenous sources of plasma lead) that is responsible for inhibiting ferrochelatase. For this outcome, plasma lead is clearly superior to body burden. Plasma lead is notoriously hard to measure, and urinary lead may serve as a less difficult marker of plasma lead, and therefore is a potential surrogate of the immediate effects of current toxicologically active lead. This needs to be highlighted in the discussion of urinary lead, along with a discussion of the difficulties.

If ferrochelatase were the only endpoint that is dependent on plasma lead, or short-term toxicologically available lead, that would be a minor point. However, for many outcomes, we simply do not know what the appropriate averaging time for lead is. For example, lead results in increased concentration of calcium in the endoplasmic reticulum, resulting in increased calcium release in response to alpha adrenergic stimulation. To the extent that this is responsible for the

effects of lead on blood pressure, that part of the response should be proportional to plasma lead concentration. Recent studies suggest that some cognitive outcomes may depend more strongly on current blood lead than previously hypothesized. The pooled results of Lanphear, strongly suggest this, for example. Hence discussions of lead biomarkers should not be limited to their ability to proxy for long term body burden.

P. 6.52 It is important to note that because of the way the sample was selected, cord blood lead was not associated with lower SES in the Boston study. This is a key result, which has substantial implication for interpreting the study. It is always better to control for potential confounding by sample selection rather than statistical control.

P. 6.53 The CD follows the outdated approach of reporting that there was a negative association with tooth lead, but not significant, and cautioning that reduced sample size suggests caution in interpreting the lack of significance. I agree that the small sample size makes significance less important. Indeed, given the large number of other tooth lead studies, it is almost irrelevant. The key question is effect size. In this longitudinal study, how did the effect size for tooth lead compare to the effect sizes from the cross-sectional studies that have used that metric of exposure? The statement that there was a null finding should be dropped as misleading. There was not a null finding. The investigators found a negative effect of tooth lead on cognitive function. They also found wide confidence intervals for that effect. Show us both.

P 6.53. Please mention that chance is another possible explanation for the finding that the strongest association between lead and full scale IQ was with exposure at age 2. Exposures to lead showed moderate tracking in this cohort. Random chance can decide which measurement shows the strongest association.

P. 6.55 Again, the most likely reason that the strongest association was with lead exposure at age 6 in the Cincinnati cohort, but age 2 in Boston, is chance. Given the correlations among the measures, we have poor power to discriminate among the exposure times or intervals.

Pp. 6.56-7 similarly, in discussing the Cleveland study, the CD repeatedly says lead biomarkers were or were not associated with some outcome. Presumably, they mean the association was or was not significant. Given that conclusions are going to be drawn from all of the studies collectively, it would be more useful to have the effect sizes and confidence intervals. At a minimum, you should tell the audience the direction of the insignificant associations.

In addition, alcoholism among inner city residents is associated with use of other, potentially fetotoxic drugs, such as cocaine and marijuana. Since these drugs, unlike alcohol, are illegal, it is difficult to obtain good measures of use and control for them. This would be quite important in this cohort. Please tell us if illegal drug use was controlled for, and how, in the analyses presented.

Why does the document state that the authors reported that the covariates explained more of the outcome than lead? Isn't this obvious? Of course they do. So what? Age explains more of lung function than ozone, for that matter. But EPA neither regulates age nor maternal IQ. Why do we care which other covariate (e.g., HOME score) had the greatest incremental R^2, or "most strongly

contributed" to child's IQ? And what does most strongly contributed to mean? Highest effect per interquartile range change in exposure? Highest incremental R^2?

P. 6.57 What does the statement "The estimated lead effect increased as a function of the level of measurement error in dentine lead variable" mean? Did adjustment for measurement error in exposure produce a steeper slope for the effects of dentine lead? This is necessarily true. Or does it mean something else?

P. 6.60 It would be useful to convert the correlation coefficients to slopes and compare them.

P. 6.61 Clarify what is meant by saying the Gomaa study is related to the Schnaas study. Just by being in the same city, or in some other way?

It is interesting to note that the effect sizes in Kosovo and the other high lead cohorts seem smaller than the effect sizes in Boston and other low lead areas (although no effect sizes are reported for Sydney). This is consistent with the steeper slopes at lower levels observed in several of the studies.

While it is fair to point out that the NHANES analyses did not control for HOME score, it is also fair to point out that unlike most other studies, it controlled for income, as indexed by the poverty-income ratio.

P, 6.91 reports that the Inuit study population had a range of blood lead concentrations of 0.8—27.1 µg/dL. It then reports results excluding the 10% of the population with blood lead levels above 101 µg /dL. I think a decimal slipped somewhere.

P. 6.107 Discussion of confounding. Here it would be useful to note that because of the middle to upper class sample drawn at Boston Lying In Hospital, and the tendency for upper class participants to live in older housing, the Bellinger study had a non-significant **positive** association between SES and cord lead, and a negative association between SES and postnatal blood lead that was considerably weaker than in most other studies. Hence the potential for confounding by SES in this study is considerably less than average, yet it reports similar or even larger effects than average.

P. 6.108 Mention here that the proper way to address the possibility that lead may be on the causal pathway of the association between social class and IQ, but that there may be other pathways that need to be controlled, is to use structural equation models, but this has not generally been done (except for Christchurch).

P. 6.112 Why is the WRAT resistant to lead? The literature in children suggests that reading is not independent of lead. This would seem to make the recommendation to control for reading test results in examining other cognitive results in adults questionable.

Given the age of the NAS participants, their high bone lead levels may reflect general population exposure in the 1960's and 1970's when environmental lead levels were higher and not some

deviation from a "general population" sample. Very few of the participants had employment that results in high occupational levels.

The NAS is well characterized for chronic medical conditions, through an every-three-year physician interview and all-day medical examination. Education is measured and controlled for in NAS studies when significant. It should be noted that for a medical condition to confound the association of lead with cognition, it must not only be correlated with cognition, but with lead.

P. 6.128 The statement that there is no consistent evidence of effects in adults if competing risks are taken into account is unsupportable. It was earlier hypothesized by the author that uncontrolled covariates might confound the associations. Hypotheses are not facts. No evidence is presented that there is confounding, and to have a statement conclude that confounding must exist in the absence of evidence is at odds with the scientific method.

P. 6.164 The word race is here in parenthesis, whereas it is not in the discussion of IQ effects. Be consistent. Also, given the proven racial differences in sensitivity to salt and to certain cardiovascular mechanisms, the implication of the quotation marks that the term has no meaning is clearly false.

P. 6.165 It should be mentioned that the British Regional Heart Study had very little power to detect an association of lead with heart disease of the magnitude that would be expected given the magnitude of the association between lead and blood pressure.

P. 6.165 While it is true that blood lead reflects both exogenous and endogenous lead, until recently; environmental lead levels were high enough so that exogenous lead dominated blood lead, except under certain circumstances, such as pregnancy, etc. Hence, for studies before the mid 1990's or in countries where leaded gasoline was phased out later, the cautions on this page are overstated. For newer studies, this is a fair point, but many recent studies have used bone lead levels as exposures.

P. 6.168 states that all models included age, age-squared, BMI, race, family history of hypertension, cholesterol, and tricep skinfold, and stratified by sex. As a comment it is stated that the stepwise regression procedure used may have deleted potential confounders because of the well known problems with stepwise regression. This is conceptually true, but in the absence of even speculation as to a confounder (correlated with blood pressure and lead) seems rather theoretical to warrant such caution.

P. 6.168 The insistence on reporting that 'no model diagnostics were reported' for most of these studies is inconsistent with the rest of the CD, where most of the studies of most of the outcomes do not report the model diagnostics discussed here, and are not singled out for such attention. Be consistent. Also, some of the studies report results of multiple different models (e.g., Den Hond et al., Pirkle et al.), and the sensitivity of the results. Such approaches are alternatives to model diagnostics.

General Comment: While the section on cognition in children repeatedly makes mention of the animal toxicology that supports the epidemiologic findings, this is totally absent in the discussion

of lead and blood pressure/cardiovascular disease. But lead has been shown experimentally to effect multiple cardiovascular endpoints, and these findings need to be cross mentioned here.

P. 6.280 Marcus and Schwartz published a nonlinear model relating lead to EP based on a toxicokinetic model, which should be included in Table 6.9.1

P. 6.316 The Schaumberg study is described as being in middle-aged males, with ages from 60-90. I agree with this definition of middle age, but my younger colleagues may differ. Of course, they are children.

P. 6.322 Exposure misclassification. This discussion needs to be more focused on epidemiologic implications and not exposure implication. Remember that in a multiple regression it is the variation in lead about its mean that is correlated with variations in outcomes about their means. Hence, a downward bias in absolute levels, such as the stated underestimate in true brain lead levels, is irrelevant. Mean differences disappear, because it is only variations about the mean that contribute to the association. The real issue is how variable the exposure error is. If blood lead is an estimate of brain lead with a great deal of variance, there will be substantial downward bias in the estimated effect of lead. In general there needs to be more discussion of the errors in variables theory from statistics, to clarify the effect of measurement error. Calculation of likely attenuation factors for a plausible range of error variation, to show the possible extent of bias, would be useful here. Some discussion of whether variations in instantaneous blood lead about "true" lead exposure are Berksonian errors or not would also be relevant.

P. 6.325 repeats the error I noted earlier of questioning the validity of a reported association based on the measurement error in the outcome. Since this measurement error can only bias downward the t-statistic for the association, it is not a possible explanation of why a significant effect was found, and therefore cannot call the association into question.

P. 6.348 Very nice application of basic risk assessment for the cardiovascular effects. I would suggest one further step. Given the reduction in risk for a 5 μg/dL drop in blood lead per 100,000 population, on can easily calculate, based on the latest NHANES data, the reduced number of cardiovascular events per year if we lowered blood lead levels a further 1 μg/dL. I believe this will be quite a large number.

Joel Schwartz

Comments on Chapter 4

Chapter 4 represents the transition between the description of sources, i.e. emissions, and the description of the association between biomarkers of dose (blood lead, bone lead, etc) and health in Chapters 5 through 7. As such it represents the key issue of how we get from estimated emissions to estimated blood lead, etc. There are important issues in this transition that are completely missing from the chapter.

First, how do we get from air emissions to concentrations in dust, soil, air, food, etc? Most air lead is absorbed through these pathways, and not direct inhalation. This involves deposition models, dispersion models, etc, which are not discussed. How much does a given amount of air lead contribute to food lead, dust lead, soil lead? This needs to be remedied. This problem must be solved, no matter how we proceed to estimate the effect of lead in these media on lead in blood.

Second, the description of how we get from lead in media to blood lead is restricted to the use of models. There is a large literature using empirical data on lead in various media and blood lead, and regression models that estimate the blood lead/media lead slope for each media, controlling for the other media. There is also an international pooling project of such studies, which needs to be described and discussed. EPA simply cannot ignore the empirical studies and rely solely on the models. The argument that such approaches are "limited to the situations where they were estimated" is no more valid than the argument that the IUEBK model is limited to the situations where it was validated. The regression models are estimated from a wide variety of locations, probably wider than the situations used to validate the IUEBK model. In addition, unless there are interactions between the effects of exposure in different pathways, or severe undetected nonlinearities, the regression models should generalize just fine. The blood lead levels of interest are near those where the models were estimated, and low enough that nonlinearities (which were examined in the pooling project) and interactions are unlikely to be important.

Finally, the current models have been validated for children, whereas EPA will need to do risk assessment for adults as well. There is apparently a crude model for adults used by Superfund. This should be discussed, because the finding of associations between lead and blood pressure makes health effects in adults an important question.

As I noted in oral commentary, the chapter needs to better describe the literature on water lead exposure.

<u>Additional Comments on Chapter 6</u>

I disagree with the comment that vocabulary or reading scores need to be controlled for in the studies of adult cognition. Controlling for them controls for a measure of baseline cognitive performance that should improve the model R^2, and hence power. This is presumably why it is recommended. However, if these scores are uncorrelated with bone lead, their omission will not result in confounding. If these scores are correlated with bone lead, that correlation may represent the effect of lead. The CD argues that these are conserved resistant properties. But this ignores the literature that tooth lead was associated with reading disability in high school from the follow-up of Needleman et al. Reading disability in high school likely translates into reading disability later in life. In general, examining the summary in this chapter about cognitive effects on children one sees evidence of association of lead with a variety of cognitive outcomes that are recommended as controls for adult cognition.. These outcomes have been associated with lead exposure, and hence it is inappropriate to control for them as potential confounders.

Flegal and Patterson's study of bone lead in pre-industrial native Americans would be useful to cite in the discussion of thresholds and "low level" effects, since they indicate that even the 2 µg/dL levels now seen are not truly low.

Threshold Argument: Following the discussion of all the factors (genetic, iron deficiency, etc.) that modify susceptibility to lead, it would be worth pointing out that the implication is that if there were thresholds in individuals, the distribution of those thresholds in the population would be expected to be wide, and hence one would not expect to see a threshold in the population average dose response curve.

Dr. Frank Speizer

Lead CD, December 2005, Draft: Chapter 6 General Comment & Charge Questions
Discussant: Frank E. Speizer

General Comment:

The chapter is well organized and progresses well, in detail through the biologic measures of exposure through the wide variety of health effects. Of concern is that because such an abundance of biologic markers of exposure exist the authors seem to have simply "left out" in this chapter any discussion of sources of exposure. For most readers it is obvious that lead is a multimedia pollutant, and this is well discussed in Chapters 2-4; however, it seems to this reader if one were to focus only on this chapter (and maybe the Toxicology Chapter 5) the sources of exposure are missing. I would suggest that a very brief discussion, perhaps taken from or expanded with words from the end of Chapter 2, Figure 2.6, be considered as part of the introduction to this chapter.

Although I indicate that the chapter is well organized, there is a problem. Because it appears that different writers seem to have written on the different disease outcomes there is considerable overlap on the discussion of the biomarkers in each section. In addition, the writers are clearly using many of the same studies in which multiple outcomes have been considered. The studies are therefore being mentioned in each section as though they have not been discussed before. In fact, this might be handled by one discussion and cross-referencing.

There are a number of places where reference is made to the Annex Tables particularly in the biomarker discussion and in the neurobehavioral sections. In large part I agree with this approach. However, there are a number of places where a summary graph, analysis, or table in the text would be useful. This is particularly in contrast to the later sections on Renal and Cardiovascular effects where this is done.

Charge Questions:

Question F1: Differences in Biomarkers

Although the discussion of each marker seems thorough, although earlier work dating back to the 70's is not discussed, which is ok; and each marker is summarized individually, what is missing from the end of the section (at about page 6-47) is a more generally summary. The Charge question asks whether the chapter adequately addresses the issue of which exposure metric is appropriate. A summary table of each of the biomarkers, where it has been used and an estimate of its adequacy might be appropriate. I think this could easily be done and might have the added effect of pulling the various outcomes together. (Maybe this is a function for Chapter 7)?

Question F2a: Neurotoxic effects at low blood Pb levels and adequacy of discussion of influence of model selection

The effects seem to be well characterized. The consistency and heterogeneity discussed. Having the Lanphear pool analysis significantly advances the understanding and goes a long well to confirming the effects at low levels of exposure. Model selection seems adequate to me but I would defer to others more sophisticated with interpretation of log-linear with moderately sparse data.

Question F2b: Adequacy of non-neurotoxic effects

The discussion of the health effects of lead seems thorough. However, it is not clear that the discussion has focused adequately on environmental (and most particularly air sources) Most of the sections read more like a chapter in a textbook of medicine, although the tables (and text on occasions) really describe some important epidemiological studies (NHANES data). Again, the issue seems to not being adequately tied to environmental exposures.

Question F2c: Adverse or clinically significant effects.

The argument that lead is a toxic pollutant was settled over 20 years ago. Much of the discussion at that time was settled by reducing environmental exposure (lead out of gasoline) and the resulting drop in blood lead in large population samples. In adult chelating studies of individuals at "toxic" clinical levels proved that neurobehavioral effects were significant and could be reversed. The more recent studies, to this reviewer, confirm the association between relatively very low levels of biologic markers of exposure, particularly in young children, result in toxic effects. Minor changes in population averages in IQ addressed in many of these studies represent important adverse health effects and the reason for these effects need to be considered (see below as answer to question F2d). In adults operating at significantly higher levels of exposure changes in blood pressure and cardiovascular effects, again on a population basis, represent significant adverse effects. Operating as an important mechanism for these later effects, the effects on the renal system become an important pathway of effect. In addition the primary clinical effects on renal function is harder to judge until it becomes clinically significant, presumably because of relatively excess reserve in clinical function that is normally present.

Question F2d: Confounders and causal inference:

Although the discussion of confounders appears appropriate in those sections where it is discussed, it is still somewhat incomplete. Part of the problem is that in the more clinical sections (renal, cardiovascular, endocrine, etc.) there are simply inadequate data to discuss. These are mostly clinical studies in which potential confounders are not adequately considered in the primary publications (nor are the primary studies designed to take all these factors into consideration). The discussion of the neurotoxic effects is far better and the important confounders are considered. However, because of the nature of most of the studies the potential for residual confounding remains. One must therefore turn to the consistency and coherence of the data to made causal inferences. One other factor that also contributes to the causal inference is that by the public health effects of reducing exposure in the 80's levels of lead biomarkers have also been reduced, and this cannot be explained by unresolved confounding. This point could be brought out more, again perhaps in Chapter 7.

Question F3: Discussion of susceptible populations:

Discussion seems adequate

Dr. Ian von Lindern

Memorandum

To: Rogene Henderson, Chair, Air Quality Criteria Document, SAB Committee

From: Ian von Lindern, Panel Member

Subject: Comments Charge Questions Section 1-4 of the AQCD First External Draft

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Overview

> **Charge Questions A1.** To what extent is the document format (*i.e.*, main chapters of the 1st draft AQCD focused on evaluative/interpretive aspects, with descriptive materials and tables presented in annexes) useful and desirable? Can the structure be further improved? If so, how?

Overall, the EPA has done an impressive job in organizing, drafting and producing the first external draft of this substantial document. Both the content and editorial quality is commendable, especially considering the topic addressed; the breadth of material that must be considered, reviewed, evaluated and integrated in a single document; and the time constraints. Section 1 lays out a cogent discussion of the purpose of the document and the process and procedures that are ahead for EPA in meeting its regulatory obligations. In that sense the document has done a good job in presenting and evaluating new information from the scientific literature that has accumulated since the last AQCD in 1986-90.

There seems to be some debate as to whether the document should be a compendium of all available information, or be limited to that data that directly addresses modifying the NAAQS. Both the 1977 and 1986 AQCD and addenda were seminal documents that, in combination with other programs, supported and led to effective regulation of lead in the environment. These efforts, in turn, substantially bettered the health and quality of life for millions of children, adults, workers, and the biosphere, both in the U.S. and globally. During the years that these environmental and public health improvements were being accomplished, these documents were utilized, referenced, critiqued and practically applied on an almost daily basis. This occurred both within and outside the inherent regulatory sphere. In that sense, these documents provided an invaluable framework for society, industry and the scientific community to develop and implement strategies to meet public health and environmental needs.

The current document will continue to serve this broader need and will be looked to and applied by those addressing lead-related and associated issues for the next decade. In deference to those uses, the EPA could, with relatively modest efforts, improve the document to serve those needs. Currently there is variability in the level of detail, presentation, discussion and nature of the several Chapters. Some Chapters provide significant evaluation and presentation of both historic and new information that has evolved since the last document. Others refer to the previous documents, particularly, where the level of data collection and sponsored research has decreased significantly since the 1980's. As a result, in some Chapters, there are long presentations of new

information that reflect the degree of new research and studies that have been published in the peer-reviewed literature. Others, particularly Chapters 2 and 3 tend to rely on older information.

There are also differences among the Chapters as to how the information is presented. The format of summarizing the understanding and knowledge through the last document in 1986, then reviewing the new studies and data, followed by a discussion of the significance in terms of regulatory needs, seems most appropriate. In several instances the analyses refer to or rely on information presented in earlier Chapters. The document would benefit by better coordinating the Chapters in line with synthesis chapter when this developed.

Chapter 2

> **Charge Questions B1.** Overall, does Chapter 2 provide adequate coverage of important chemical properties of lead and concise summarization of pertinent information on sources of Pb and Pb emissions, especially in relation to the United States? In particular, how well does Chapter 2 identify the most pertinent available datasets that contain information on emission rates for point and area sources? Also, does the discussion of available data adequately address issues such as the spatial distribution of point and area sources and emissions estimate uncertainties?
>
> Furthermore, does the discussion satisfactorily address emissions by key industrial sectors? Does Chapter 2 adequately address other important issues relating to the dispersal and/or accumulation of Pb in the environment, *e.g.*, resuspension of roadside dust or the potential for Pb to accumulate in some media, like soils, due to its relatively low mobility? (The latter fact means that fairly low air Pb concentrations have the potential to produce elevated soil concentrations over time due to wet and dry deposition.) In addition, does the chapter adequately discuss key chemical and transport related factors that should be considered in evaluating long-term buildup of Pb in the environment? Finally, are the discussions of the leaching of Pb from soil and sediment into surface and groundwater sufficiently complete for this chapter?

Relatively less new and detailed information appears in Chapter 2 in comparison to other chapters, and in relation to the types of emission and source data and environmental chemistry and transport presentations in the earlier AQCD documents. However, there have been tremendous decreases in both the magnitude of the sources and curtailing of environmental migration and transport that have effected significant reductions in exposures, absorption, biological markers, etc. These, in turn, have led to human populations with levels of lead lower than was conceivable thirty years ago. Clinical and research activities involving this evolving population has led to greater understanding of the mechanisms and adverse health effects at lower exposure levels. Sampling, monitoring and diagnostic techniques; exposure and biokinetic models; and cleanup, remediation and preventative health responses have all evolved as a result of these actions.

References are made in numerous places in later Chapters to the tremendous source, exposure and blood lead reductions achieved and the significance of these accomplishments in analyzing new material in almost every discipline. Presumably, the synthesis Chapter will make similar references. This story, however, is not obvious in the current document, particularly in some of sections of Chapter 2. It seems to indicate that emissions are of lesser concern, when the message should emphasize the reductions that have been achieved, to set the tone for the remainder of the document.

A major concern is that EPA has limited the review to *"… where information is available in the peer-reviewed literature."* Unfortunately, the best information for production data, emission information, industry transition and economic indicators is found in the trade literature and government agency records. Much of the practical knowledge that has, and continues to be developed, with regard to applying scientific findings and methods to remedial and regulatory activities is being generated in programmatic activities. These are the actions that have resulted in the dramatic reductions in releases and exposures that have been achieved since the gasoline phase-down. For the last decade, this information is accumulating within programs and professional literature at a rate probably an order of magnitude greater than that reaching the peer-reviewed journals.

It seems this information limitation would affect the ability of the Agency to assess impacts of implementing any major revision to the NAAQS. Perhaps this will be handled in the Staff Paper. But it leaves a void in the base information about sources that makes it difficult to put review of the remainder of the document in the context of — How much lead is out there? Where is it? What's it doing? Where is it going?

More of this contextual information is found throughout the other Chapters, but doesn't seem to be appropriately introduced or supported by data in Chapter 2. Answering these contextual questions seems vital to assessing the significance of atmospheric lead and the discussions and analyses in the remainder of the document.

Section 2.1 Physical and Chemical Properties

This Section is well developed and presented in an interesting manner. It could benefit from providing a few additional examples of the significance of these chemical and physical mechanisms in environmental and biological processes that could be tied to material presented in later Chapters. In particular, these physical and chemical properties could be tied to the transport discussions later in this Chapter.

Section 2.2 Sources of Lead

Section 2.2.1 Natural Sources

Most of the concentration data indicated for "background" is globally averaged. A good deal of information has been developed at various mining sites around the country and world regarding background concentrations in mineralized areas. These data are available for host rock, soils sediments. Inclusion of these data could provide perspective regarding the variability of "background".

This is a general comment that goes beyond the natural sources. Much of the presentation in this Section provides gross estimates but puts little in context of local, site-specific or industry categories that might be affected.

The last sentence on line 15, page 2-12 and first sentence on page 2-13 should provide some reason for the observed differences.

The discussion for lead 210 on p 2-14 seems disproportionate to the relative significance of this isotope in natural systems, as opposed to its significance as a tracer.

Section 2.2.2 Stationary Sources

This section would benefit greatly by providing perspective for the various discussions undertaken. The magnitude, values, percentages, etc. should be put in context. This should include an historic and national context, especially for the last 40 years that EPA has been active in effecting the changes. With regard to future users of this document, it should also provide global context that relates how other countries' emissions and releases compare to ours and a local perspective acknowledging problem areas in the U.S and elsewhere. Summary Tables to support the discussion would be useful.

A more developed historic summary of primary and secondary production for both the U.S. and overseas would provide perspective regarding the shift in lead-related industrial activities, major stationary source behavior, capacities, emission factors, etc. Summary Tables to support the discussion would be useful.

More information regarding secondary production, in particular recyclers and battery recovery operations, would be beneficial. This is one area where lead usage and production is increasing and the prognosis for responsible life-cycle management is not indicated in this Chapter. Is this a potential problem that should be flagged as a research need, or would a review of industry practices show little need for regulation? Conversely, neighborhood battery reclamation is an increasing danger around the world, as more people become car owners in many developing countries. Summary Tables to support the discussion would be useful.

The *Mining and Processing* section seems limited to emissions from active mines. Among the largest sources of lead release in the U.S. today are abandoned mining operations and waste repositories. There is significant data accumulated in CERCLA and RCRA programs inventorying the amount of lead waste being managed in the U.S. today. Presenting these data would provide perspective regarding where regulatory resources should be allocated. Many of the major mining related sites, in both programs, and at unregulated sites on private and public lands represent significant sources of wind-blown or vehicle induced dusts and waterborne erosion.

This introduces the question of contaminated soils that, together with the inventory of lead paint in the U.S. housing stock, represents the largest sources of lead requiring management in the country today. These topics likely deserve a sub-section in this Chapter as it relates to their role as potential sources of lead.

Lastly, it would be more enlightening if the document were to develop and discuss a summary of lead releases (as opposed to emissions) to the environment. This should supplement a more detailed emission inventory that should also be developed. Comparing releases from the various sources, as opposed to emission inventories from point and mobile sources - in a historical summary- would provide considerable perspective regarding environmental lead.

It is important that the source categories be presented in a format that demonstrates the relative significance of the emissions and releases. This should be coordinated with the importance that these sources play in the synthesis analyses and eventual regulatory needs. The various Tables presented should be developed to support this theme.

Section 2.3 Transport Within the Environment

This Section was well developed with regard to the physics of various transport mechanisms that can result in significant migration of lead in particulate or dissolved form. This section would benefit if the discussions were prefaced with a few additions that tie the transport processes to later Chapters that discuss mechanisms, sources and receptors in the traditional contaminant migration format. For example, particulate lead generally trans-locates either as dust in the atmosphere or particles adhering to people, pets vehicles, objects etc.; or as suspended sediments in water. These particles are transported to receptors where key exposure media are house-dust, street dusts, soils etc. These particles generally end up in the soils where they reside for long periods. Water- borne particulate most often reach a sediment sink, where it is subject to both physical and dissolved phase transport.

Again, there have been numerous studies conducted in CERCLA and RCRA programs that could provide perspective on the significance of these factors in the U.S. Contaminant transport from industrial and mining sites continues to present significant exposure to large populations in developing countries. The migration of lead-based paint to house dusts and soils is an important mechanism for which a substantial amount of data has accumulated.

Summary:

This summary to this Chapter could be made more cogent by editing and making additions that preface how these data and the story it portends are used in the following Chapters. The Figures should also be selected to illustrate the same important points. Figure 2.5 should be updated as it shows that U.S. production almost returning to peak levels by 1990, where it ends, despite the phase-down. What has happened since then, how much goes to batteries today, are there releases in the life-cycle? Do we know, etc.?

Chapter 3

> **Charge Questions C1.** Does Chapter 3 provide adequate coverage of pertinent available information (especially as it pertains to the United States) on Pb exposure routes, as well as environmental Pb concentrations, including those in air, drinking water, food, soils, and dust? Also, does the chapter delineate adequately interconnections between airborne Pb and its potential contributions (via secondary deposition) to Pb in other media (*e.g.*, indoor dust)?
>
> Moreover, given the potential importance of historical deposition of Pb from mobile sources, does the chapter adequately identify key sources of information characterizing the magnitude and distribution of lead soil concentrations near roadways in urban, suburban and rural areas? Also, given the importance of characterizing "background" Pb concentrations in conducting health/ecological impact analyses (where background refers to both natural and generalized anthropogenic contributions as distinct form specific point sources), does the chapter adequately denote key sources of information characterizing existing "background" Pb levels in urban, suburban and rural/pristine areas?

Chapter 3 suffers some of the same shortcomings noted for Chapter 2. EPA has confined the review to the peer-reviewed literature when the most advanced work accomplished in defining exposures, pathways and estimated doses from environmental sources has occurred in regulatory applications in CERCLA and HUD remedial activities. For the AQCD and follow up standard setting process, EPA should either take advantage of the wealth of information available from these regulatory activities, or point out the scarcity of peer-reviewed information suitable for decision-making. These data sources and experiences could be considered in either the AQCD or Staff Paper. However, it would not be prudent to limit the combined analyses to the relatively obscure and less-representative studies that have reached the peer-reviewed journals. In the event that EPA is restricted from utilizing this extensive experience in crafting effective regulations, the scarcity and short-comings of information available from journal articles should be noted.

It also seems that that the key message Chapter 3 should leave with the Administrator and critical reviewers is not clearly articulated. Chapter 3 should take the source, release and environmental transport information from Chapter 2 and emphasize and quantify those pathways that lead to critical exposures to humans and environmental receptors. In regard to human health; residual soil and paint, and (as noted for Chapter 2) a poorly-defined industrial sector contribution are the largest sources in this country today. The scientific consensus seems to be that dust is the key environmental media offering excess exposures today. Airborne lead plays a key transport role in effecting dust concentrations and loading through deposition. The intermediate air lead relationships between the source and the dust variables are the key component that a new standard will have to address. Understanding and quantifying the accumulation rates of deposition is a critical unknown. How much source control will have to be exercised will be determined by the relationship between dust loadings and blood lead levels (and, as noted below, other contributors to lead intake).

Chapter 3 would benefit from additional structuring that illustrates the connections to the source descriptions in Chapter 2, then follows the critical pathways through to exposure and intake in Chapter 3, thus setting up multi-media input analysis through modeling that is presented in the following Chapter 4. These analyses have been accomplished in internally peer reviewed, or at least heavily critiqued, procedures at dozens of CERCLA and RCRA sites. The EPA should not disregard this wealth of experience in addressing risks associated with airborne lead.

On the question of dust lead measurements, there does not yet seem to be a clear consensus on the most effective methods to measure dust lead and relate it to blood lead levels. Lanphear, et al. have conducted and compared dust collection methods in a side-by-side approaches and noted that lead loading ($\mu g/ft^2$), as opposed to lead concentration (mg/kg), showed higher correlation with children's blood lead levels. Yiin et al. (2002) noted six studies of hard surfaces (i.e., floors and window sills) where loading was found to be better correlated with blood lead and two studies were cited where dust lead concentrations collected by vacuum sampling of carpets were better. The latter was also noted at the Bunker Hill Superfund Site in Idaho (von Lindern, et al. 2003a, and von Lindern, et al. 2003b). There is apparently some confusion in citing the Bunker Hill findings in these journal articles as both should be referenced, one focusing on dust:soil relationships and the other on dust/soil:blood lead relationships.

Chapter 4

> **Charge Questions D1**. How well does Chapter 4 concisely characterize key information on: (a) the evolution and key features of important available approaches to the modeling of external Pb exposures and their impacts on internal Pb body burdens; and (b) the status of model evaluation efforts, *e.g.*, PBPK model code verification and comparisons of model-predicted versus observed impacts on blood or bone Pb distributions of particular lead exposure scenarios for affected population groups? Also, does Chapter 4 sufficiently characterize the ability of different models to handle key factors related to lead exposure modeling, including: temporal variation in external exposure profiles; low level lead exposure; multi-pathway lead exposure; and the contribution of historical/artifact lead exposure in influencing blood lead levels?
>
> Furthermore, given that the October 2005 SAB review of the AALM suggested that further model validation and verification was needed before the AALM should be used in support of regulatory development, does Chapter 4 clearly identify which alternative models (*e.g.*, IEUBK, O'Flaherty) should be used for adult and/or child modeling instead of the fledgling AALM? In addition, does Chapter 4 adequately identify the strengths and weaknesses of the recommended models in modeling adult and child populations? Finally, overall, how can Chapter 4 be improved without notable extension of length?

Two main points should be more clearly articulated in Chapter 4. Those points are inter-related in an important context. The first point is that lead is a multimedia contaminant as illustrated in Chapter 3. The second point is that later Chapters indicate that there is no apparent threshold for deleterious effects and adverse irreversible outcomes are likely at low levels. As a result, to evaluate, develop and implement reasonable interventions and regulations, EPA will need to effectively analyze exposures and blood lead responses at extremely low levels in multiple media. At present, this can only be accomplished through modeling. This Chapter should rigorously critique the available models, as it does. It should also point the regulators to the most effective and useful models with the best track record. That is not clear in the current version.

In Chapter 4 the difficulties of relying on the experience reflected in peer-reviewed journal articles needs repeated. The IEUBK model has been employed at dozens of CERCLA/RCRA sites and EPA has maintained internal review groups to monitor and critique these applications. The AALM is not currently, and likely will not be in the context of the AQCD timeframe, developed to a point sufficient to use in regulatory activities. The other models do not have the depth of application to real-world situations, nor have they been relied upon to make significant health decisions and resource commitments. The EPA should make an effort, in either the AQCD or Staff Paper, to convey this experience and lessons learned to reviewers and decision-makers in this process.

The conflict between peer-reviewed literature and practical experience in utilizing scientific information to effect environmental policy has been an enduring difficulty. Much of the front-line and more innovative work with regard to reclamation, remediation exposure reduction and source management is being accomplished in programmatic activities. Concerns have been voiced that this information is not appropriately disseminated, is not subject to peer-review, and may or may not apply the best scientific methods. At the request of Congress, the National Research Council of the National Academy of Science recently completed an extensive review of the adequacy of scientific methods employed at the Bunker Hill Superfund Site in northern

Idaho. The NAS was specifically charged with addressing the adequacy of the IEUBK model and EPA's use of the model. That report entitled *Superfund and Mining Megasites-Lessons from the Coeur d'Alene River Basin,* (NRC 2005) evaluates this problem with respect to a major lead site that has played a historically significant role in the development of the NAAQS over the last thirty years. (The study Yankel, et al. 1977 was one of the those selected to define the blood lead:air lead ratio for the current NAAQS. The NAAQS was subsequently challenged in federal court on the basis of the scientific adequacy of Yankel, et al. and was upheld). Some of the lessons learned and references utilized in the NAS review could be applicable to the preparation of this document. Von Lindern, et al. 2003a summarizes the blood lead:soil/dust relationships, applies the IEUBK model to more than twenty years of remedial and health response activities, and compares mechanistic and quantitative models in explaining those relationships.

Lanphear, B. P., M. Emond, et al. (1995). "A side-by-side comparison of dust collection methods for sampling lead- contaminated house dust." Environ Res **68**(2): 114-23.

Lanphear, B. P., T. D. Matte, et al. (1998). "The contribution of lead-contaminated house dust and residential soil to children's blood lead levels. A pooled analysis of 12 epidemiologic studies." Environ Res **79**(1): 51-68.

National Research Council of the National Academies (NAS) (2005). Superfund and Mining Megasites-Lessons from the Coeur d'Alene River Basin.

von Lindern, I., S. Spalinger, et al. (2003a). "Assessing remedial effectiveness through the blood lead:soil/dust lead relationship at the Bunker Hill Superfund Site in the Silver Valley of Idaho." The Science of The Total Environment **303**(1-2): 139-170.

von Lindern, I. H., S. M. Spalinger, et al. (2003b). "The influence of soil remediation on lead in house dust." The Science of The Total Environment **303**(1-2): 59-78.

Yiin, L. M., G. G. Rhoads, et al. (2002). "Comparison of techniques to reduce residential lead dust on carpet and upholstery: the New Jersey assessment of cleaning techniques trial." Environ Health Perspect **110**(12): 1233-1237.

Yankel, A. J., I. H. von Lindern, et al. (1977). "The Silver Valley lead study: the relationship between childhood blood lead levels and environmental exposure." J Air Pollut Control Assoc **27**(8): 763-7.

Dr. Barbara Zielinska

Comments on the EPA NCEA-RTP Air Quality Criteria Document for Lead, First External Review Draft
Chapter 2: Lead Chemistry, Sources and Transport
Barbara Zielinska

In general, Chapter 2 is very well written and summarizes adequately pertinent information regarding chemistry, natural and anthropogenic sources and transport of lead in the environment. However, the information regarding lead emissions from important industrial sources seems to be somewhat outdated. For example, Pb emission data from coal combustion, fuel oil combustion and some metallurgical processes relay mostly on older references (such as Pacyna, 1986). These data are limited and may no longer be applicable. If adequate peer-review literature data do not exist, the use of publicly available reports and reliable compilation of data is justified.

The chapter identifies available sources of information on emission sources and emission inventory and points out their uncertainties. However, although the limitations of AP-42 guidelines and other EPA emission inventories are mentioned in general, the reader is not informed as to why these data are not applicable. Usable emission and source characterization data are critical and the need to have them updated has to be emphasized. In addition, although data concerning lead particle sizes are scattered through different sections, a summary section or table would be useful.

The transport of lead within the environment is covered very thoroughly. I find the discussion regarding the accumulation of lead in soil and sediments adequate and informative in term of the long-term build-up of Pb concentrations in the environment.

Specific comments:

1. Page 2-1, lines 23-25: this sentence needs revision – perhaps "…that forms a protective…"
2. Page 2-1, line 29: amount of oxygen
3. Page 2-9 and 2-10: the terms used in equations 2-2 and 2-3 need to be explained
4. Page 2-15, lines 29-30: the range of emission rates from the blast furnace seems to be very high. Also, the reference is rather outdated (1989).
5. Page 2-14, line 28 and page 2-68, line 6: I find the terms like non-human animals and human animals rather strange…
6. Page 2-25-2-26: the information concerning Pb emissions from fuel oil combustion relay mostly on older reference (Pacyna, 1986).
7. Page 2-48, line 2: Equation 2-1? I suppose 2-5 is meant.
8. Page 2-52, line 6: is the dry deposition more important than wet deposition in marine areas?
9. Page 2-56, Figure 2-3: the figure capture mentions three resuspension rates, but the figure legend shows four
10. Page 2-72, Figure 2-5 is rather poor quality and difficult to read.
11. Page 2-74, Figure 2-7. I suppose wet and dry deposition is also important for water surfaces.

NOTICE

This report has been written as part of the activities of the U.S. Environmental Protection Agency's (EPA) Clean Air Scientific Advisory Committee (CASAC), a Federal advisory committee administratively located under the EPA Science Advisory Board (SAB) Staff Office that is chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC is structured to provide balanced, expert assessment of scientific matters related to issue and problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. CASAC reports are posted on the SAB Web site at: http://www.epa.gov/sab.