



February 15, 2006

MEMORANDUM

SUBJECT: CASAC Review of First External Review Draft Lead Air Quality Criteria Document (1st Draft Lead AQCD)

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As part of the U.S. Environmental Protection Agency's (EPA) ongoing periodic review of the National Ambient Air Quality Standards (NAAQS) for Lead (Pb), EPA's National Center for Environmental Assessment, Research Triangle Park (NCEA-RTP) Division has undertaken preparation of an updated revision of the EPA document entitled, *Air Quality Criteria for Lead (First External Review Draft), Volumes I and II* (EPA/600/R-05/144aA-bA, December 2005). This first draft lead air quality criteria document (AQCD), consisting of two volumes, was made available for public comment by posting on the Agency's NCEA Web site at the following URL: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=141779>. Also, CD-ROM and hard (paper) copies of the 1st Draft Lead AQCD were sent to members of the Clean Air Scientific Advisory Committee's (CASAC) newly-formed Lead Review Panel (Panel). This 1st Draft Lead AQCD is scheduled to undergo peer review by the Panel at a public meeting to be held February 28 – March 1, 2006 in Durham, NC.

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 on health and welfare effects associated with the presence of lead in the ambient air. The Lead AQCD will be used by EPA's Office of Air Quality Planning and Standards (OAQPS) staff to prepare a Lead Staff Paper entitled *Review of the National Ambient Air Quality Standards for Lead: Policy Assessment of Scientific and Technical Information*. That Lead Staff Paper will evaluate the policy implications of key studies and scientific information assessed in the Lead AQCD and present OAQPS staff evaluations of standard-setting options for the EPA Administrator to consider in deciding whether to revise the Lead NAAQS.

An earlier document, the *Project Work Plan for Revised Air Quality Criteria for Lead* (U.S. EPA, 2004), described the approach to be used in preparation of the subject Lead AQCD and provided an overview of the planned organizational structure, format, and intended general contents of the document. That work plan was discussed in a teleconference consultation with the statutory (chartered) CASAC in February 2005. Preparation of the subject 1st Draft Lead AQCD benefitted both from that CASAC consultation and from peer-consultative workshop reviews of preliminary draft AQCD materials obtained by NCEA/RTP in mid-2005.

The main purpose of this “charge memo” is twofold, both: (a) to help orient CASAC Lead Panel reviewers to the overall structure and content of the 1st Draft Lead AQCD and the key issues addressed therein; and (b) to help focus their review on matters of most importance to assist the Agency in improving the quality of the document. Accordingly, brief overviews concerning certain key features and issues addressed by the 1st Draft Lead AQCD are provided below, along with pertinent charge questions posed in relation to a number of important topics.

We look forward to discussing the 1st Draft Lead AQCD with the CASAC Lead Review Panel at the upcoming February 28 – March 1, 2006 public meeting. Should you have any questions regarding the First External Review Draft of the Lead AQCD, please feel free to contact me at phone: 919-541-4173, or via e-mail at: grant.lester@epa.gov.

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 from 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 a critical loads? Is there important additional material that should be covered in the next draft of the chapter?