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SUMMARY REPORT OF THE PEER REVIEW MEETING FOR EPA'S DRAFT REPORT, *PROPOSED MODELING APPROACHES FOR A HEALTH-BASED BENCHMARK FOR LEAD IN DRINKING WATER*

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NOTICE

This report was prepared by Eastern Research Group, Inc. (ERG), a U.S. Environmental Protection Agency (EPA) contractor, as a general record of discussion during the Peer Review Meeting for EPA's Draft Report: *Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water*, held June 27-28, 2017, in Washington, DC. This report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of meeting participants.

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1. INTRODUCTION

1.1 Background

The U.S. Environmental Protection Agency's (EPA's) Office of Water is considering revisions to the National Primary Drinking Water Regulations for Lead and Copper (LCR) in order to improve public health protection. As one part of this process, Eastern Research Group, Inc. (ERG), an EPA contractor, organized an independent peer review of EPA's Draft Report: Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water. This draft report presented three potential scientific modeling approaches the Agency had developed to understand the relationship between lead levels in drinking water and blood lead levels for sensitive life stages such as formula-fed infants and children. EPA developed these models in response to a recommendation from EPA's National Drinking Water Advisory Council's (NDWAC) Lead and Copper Rule Working Group, which was formed to provide advice to the Administrator on recommendations to strengthen public health protections of the LCR.

Specifically, NDWAC recommended that the Agency establish a *household action level*[1] "based on the amount it would take an infant to have a blood lead level (BLL) greater than five micrograms per deciliter (µg/dL) based on consumption by an average, healthy infant of infant formula made with water"[2]. NDWAC recommended that water systems be required to notify the consumer, the state drinking water program, and the local public health agency if this level were exceeded, with the expectation that individuals and local health officials will use this information to take prompt actions at the household level to mitigate lead risks.

EPA has not yet determined the specific role of a health-based benchmark for lead in drinking water in the revised LCR, although the Agency saw value in providing states, drinking water systems, and the public with a greater understanding of the potential health implications for vulnerable populations of lead in drinking water. EPA anticipated that the proposed rule would consider the health-based benchmark approach recommended by NDWAC, and that this value could also help inform other potential elements of a revised rule – including public education requirements, prioritization of households for lead service line replacement or other risk mitigation actions at the household level, and potential requirements related to schools.

The Agency developed three approaches that model lead in drinking water's effect on BLLs using a range of exposure scenarios. These three approaches were the subject of the peer review described in this report. All three approaches employ the Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children. Approaches 1 and 2 are individual-based approaches that look at the increase in the probability that a child would have an elevated BLL and a child's incremental increase in BLL, respectively. Approach 3 is a population-based probabilistic approach that evaluates the drinking water lead concentrations that would keep BLLs at particular percentiles of a simulated national distribution of different aged children. It uses the probabilistic Stochastic Human Exposure and Dose Simulation (SHEDS) Multimedia model coupled with IEUBK.

1.2 Peer Review Process

As a contractor to EPA, ERG organized this external independent peer review. In a January 2017 Federal Register Notice (FRN), EPA initiated the peer review process by providing the draft *Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water* and draft peer review charge for public

[1] To reduce confusion with the existing LCR system-wide "action level" and because EPA has not decided the role of the health-based benchmark in a revised LCR, EPA uses the terminology "health-based benchmark" to refer to this concept.

[2] Lead and Copper Rule Working Group. 2015. Report of the Lead and Copper Rule Working Group To the National Drinking Water Advisory Council. P. 37. https://www.epa.gov/sites/production/files/2016-01/documents/ndwaclcrwgfinalreportaug2015.pdf

comment. The FRN also provided criteria for reviewer expertise sought for this review[3], and invited interested members of the public to nominate qualified individuals as candidates for ERG's consideration when selecting reviewers. Nominations were sent directly to ERG.

Concurrent with the nomination process, ERG conducted its own independent national and international search for candidates with expertise described in EPA's selection criteria. ERG contacted and obtained further information from all nominees and ERG-identified candidates to confirm their interest in and availability for conducting the review, qualifications, lack of conflict of interest, and impartiality. This process generated a pool of qualified candidates.

In March 2017, EPA published a second FRN that provided the names, affiliations, and biographies of all candidates in the pool. EPA requested that interested members of the public provide any relevant comments and information on their expertise and qualifications for ERG's consideration in selecting final reviewers. After carefully considering all comments received, ERG selected from the candidate pool the following eight reviewers. Collectively, these reviewers best covered the expertise areas required by EPA's selection criteria, as well as (where feasible) other relevant areas of expertise suggested in the public comments:

- Panos Georgopoulos, Ph.D., Rutgers University
- Philip Goodrum, Ph.D., Integral Consulting, Inc.
- Ian von Lindern, Ph.D., TerraGraphics International Foundation
- Anne Loccisano, Ph.D., Exponent
- Marc A. Nascarella, Ph.D., Massachusetts Department of Public Health
- Michèle Prévost, Ph.D., Polytechnique Montreal
- P. Barry Ryan, Ph.D., Emory University, Rollins School of Public Health
- Kathleen L. Vork, Ph.D., California Environmental Protection Agency, Office of Environmental Health Hazard Assessment

EPA announced reviewer names and affiliations in a third FRN, along with details of the peer review meeting, which was open to the public as observers. A list of reviewers and their biographies are provided in Appendix A.

The review then proceeded in two stages. In the first (pre-meeting) stage, ERG provided reviewers with the EPA's Draft Report: *Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water*, an in-press paper[4] authored by EPA staff, as supplemental information, and the Agency's charge to reviewers (Appendix B). The charge provided specific questions that reviewers should address and noted that the Agency was seeking comments on the scientific aspects of the potential modeling approaches to associate lead in drinking water with BLLs in children. The charge also explained that the values applied in the approaches and the results derived from the models were for illustrative purposes only, did not indicate EPA policy decisions, and were not, in and of themselves, the focus of the peer review. ERG also provided reviewers with a summary of the public written comments on EPA's draft document, along with the complete set of original public comments in EPA's docket. Reviewers then worked individually to prepare written pre-

[3] As stated in the FRN, candidates should possess a strong background and demonstrated expertise in one or both of these areas: (1) physiologically based pharmacokinetic (PBPK) modeling, particularly with regard to lead, and (2) environmental lead exposure analyses, particularly with regard to probabilistic modeling.

[4] Zartarian, V.G., J. Xue, R. Tornero-Velez, J. Brown. 2017. Children's Lead Exposure: a Multimedia Modeling Analysis to Guide Public Health Decision-Making. Environmental Health Perspectives, In Press, DOI number: 10.1289/EHP1605.

meeting comments in response to EPA's charge questions. ERG provided these pre-meeting comments to all reviewers and EPA a few days prior to the meeting for their use in preparing for the peer review meeting.

In the second stage, ERG facilitated a 1½-day peer review meeting, on July 27-28, 2017, at a Washington, DC, venue. The meeting was attended by 76 observers (Appendix C), including ERG and EPA staff and members of the public. A total of 33 observers attended in person and 43 others listened to all or parts of the meeting via teleconference.

Appendix D provides the meeting agenda. The meeting format included EPA welcome remarks, EPA presentation of the three models (Appendices E and F), and oral public statements (Appendix G), followed by reviewer discussions. After the meeting, reviewers submitted their individual post-meeting comments (Appendix H) to ERG[5].

This report summarizes the meeting proceedings as follows:

- Sections 2 through 8 provide a detailed summary of the entire meeting. Section 2 presents the opening remarks; Sections 3 through 7 summarize the reviewers' discussions in response to each of the five charge questions; and Section 8 presents reviewer individual closing remarks.
- The appendices provide the following information: List of Peer Reviewers and Biographical Sketches (Appendix A), Charge to Peer Reviewers (Appendix B), List of Observers (Appendix C), Peer Review Meeting Agenda (Appendix D), EPA Overview of Approaches 1 and 2 (Appendix E), EPA Overview of Approach 3 (Appendix F), Public Statements (Appendix G), Reviewer Post-Meeting Comments (Appendix H)[6], Reviewer Post-Meeting Comments Organized by Charge Question (Appendix I), and Additional EPA Sensitivity Analyses (Appendix J).

2. OPENING REMARKS

Jan Connery (ERG), the meeting facilitator, opened the meeting by welcoming the reviewers (Appendix A) and observers (Appendix C). Observers included the EPA document authors, other EPA staff, and interested members of the public. Connery asked the reviewers to introduce themselves.

Connery reviewed the meeting agenda (Appendix D). She noted that, to prepare for the meeting, reviewers worked individually to develop written pre-meeting comments. These comments were preliminary, to set the stage for the discussions. After the meeting, each reviewer would revise his or her written comments to reflect any change in views or additional relevant details resulting from the discussions in order to provide a final written record of each reviewer's individual comments (Appendix H).

Connery clarified that all meeting discussions would be conducted by the peer reviewers only. Reviewers could request, and EPA could offer, clarifications where necessary and relevant. Reviewers could also request clarifications from public commenters. Finally, she noted that consensus was not a goal of the meeting. Rather, all reviewer comments would be those of the individual peer reviewers.

Connery then introduced Eric Burneson, Director for the Standards and Risk Management Division in EPA's Office of Water.

[5] All reviewers except Dr. Prévost provided post-meeting comments.

[6] Appendices H and I provide post-meeting comments for all reviewers except Dr. Prévost.

2.1 EPA Remarks

Welcome Remarks

Burneson welcomed the reviewers, and thanked them for their participation on the peer review panel. He noted the importance of this scientific discussion to inform potential revisions to the Lead and Copper Rule, and briefly summarized the goal of the proposed modeling approaches.

EPA established a Maximum Contaminant Level Goal of zero for lead in drinking water when the rule was promulgated in 1991. The current rule also includes an action level of 15 parts per billion (ppb), which is based on feasibility. This treatment technique rule was designed to reduce lead levels to the extent feasible through corrosion control, public education, and lead service line replacement. As part of EPA's revisions to the Lead and Copper Rule, the Agency sought broad-based recommendations from NDWAC on how to improve public health protection. One of NDWAC's recommendations was for EPA to develop a "household action level" that would trigger a notification to residents, state regulatory authorities, and local public health authorities if unacceptable levels of lead were detected.

EPA is considering this recommendation and has developed several methodologies to inform a health-based benchmark for lead that could be considered within the context of the revised Lead and Copper Rule. NDWAC recommended a very specific construct for this methodology (i.e., a household action level based on the amount of lead it would take for an infant's blood lead level to exceed 5 µg/dL based on consumption of formula reconstituted with water by an average healthy infant), but the Agency is considering a broader range of potential modeling applications. EPA has asked the peer review panel to evaluate the scientific merit of the Agency's proposed modeling approaches.

Burneson thanked EPA scientists for their hard work in preparing these alternative methodologies. He introduced Ahmed Hafez and Valerie Zartarian to the panel and recognized a number of other EPA scientists (i.e., Jianping Xue, Lameka Smith, Lisa Christ, Mike Tornero-Velez, Michele Burgess, Jim Brown, Michael Goldberg, Lisa Huff, and Bob Cantilli). Burneson also thanked the observers and public commenters for their participation, as well as ERG for facilitating the meeting.

EPA Overview of Approaches 1 and 2

Connery then introduced Dr. Ahmed Hafez, also with the EPA Office of Water's Standards and Risk Management Division. Hafez's presentation, entitled "Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water," is provided in Appendix E.

Hafez provided a summary of the expert peer review process and noted that this peer review will inform future consideration of a health-based benchmark for the Lead and Copper Rule (slide 2). Hafez then introduced the concept of predicting changes in children's BLLs using the IEUBK model for three age groups of interest (i.e., 0 to 6 months, 1 to 2 years, and 0 to 7 years); exposure pathways (e.g., drinking water exposure only, aggregate exposures); and BLL thresholds (i.e., 3.5 µg/dL and 5 µg/dL) (slide 2). After a brief introduction of the two modeling approaches, Hafez presented additional background information on the IEUBK model, including the four main components of the model (i.e., exposures, uptake, biokinetic, and variability) and the required modeling inputs (e.g., concentration of lead in soil, maternal BLL, drinking water rate) (slides 4 through 9). He noted that EPA modified some of the IEUBK input parameter values to reflect national modeling and to simplify comparisons across the different modeling approaches.

Hafez defined Approach 1 as the increased probability of elevated BLLs for an individual child and Approach 2 as the incremental change in BLLs for a representative child, and noted that the two approaches use the same data but offer different output interpretations (slides 10 through 12). During model development, EPA created different baseline lead exposure profiles without drinking water exposure, and then the effect of incrementally adding lead exposure from drinking water was explored. Modeling outputs were presented for different age groups and exposure scenarios. The lowest drinking water concentration required to incrementally increase BLLs or increase the probability of an elevated BLL was predicted for the 0- to 6-month-old age group (slide 11). Further details are provided in Appendix E.

EPA Overview of Approach 3

Connery then introduced Dr. Valerie Zartarian, with EPA's Office of Research and Development. Zartarian's presentation, entitled "Overview of the SHEDS-IEUBK Probabilistic, Population-Based Multimedia Exposure Modeling Analysis for Lead in Drinking Water," is provided in Appendix F.

Zartarian noted that the goals of Approach 3 were to determine drinking water lead concentrations that could keep specified percentiles of national BLL distributions of different aged children below a defined benchmark BLL, and to evaluate model-predicted BLLs against CDC National Health and Nutrition Exposure Survey (NHANES) BLL data to quantify the relative contributions of each exposure pathway and to identify key inputs with sensitivity analyses. She noted that this modeling approach is focused on a national population-based distribution and not vulnerable high-risk populations. To accomplished these goals, EPA coupled the SHEDS-multimedia model, which probabilistically simulates exposures, with the IEUBK model, which estimates BLL, to harness strengths of each model and advance the science.

Zartarian noted that EPA evaluated scenarios for different age groups (e.g., 0 to 6 months, 0 to 7 years), exposure pathways (e.g., drinking water exposure only, aggregate exposures), BLL thresholds (i.e., 3.5 µg/dL and 5 µg/dL), and percentiles of the population (i.e., the 95^{th} and 97.5^{th} percentiles). EPA developed batch and regression approaches to couple the models and compiled available data to develop distributions for soil, dust, air, and food concentrations and exposure factors. EPA compared predicted modeled BLLs to measured BLLs from CDC's NHANES database and EPA's National Human Exposure Assessment Survey (NHEXAS) database. EPA conducted sensitivity analyses and addressed comments from a work-in-progress external peer review consult and from three external reviewers from the Environmental Health Perspectives journal. Refer to slides 2, 3, and 7 for more details.

Zartarian described EPA's SHEDS-multimedia exposure modeling framework (slides 4 through 6), EPA's iterative lead modeling process (slides 7 and 8), and the selected modeling input parameters (slide 9). She noted that results presented on slides 10 through 15 are slightly different than those shown in EPA's draft report; EPA made some recent changes to address reviewer comments from the Environmental Health Perspectives journal. Slides 10 and 11 present the SHEDS-IEUBK evaluation for the three age groups considered by EPA. Slide 12 demonstrates that the relative error was reduced when biological variability was accounted for when coupling of SHEDS and IEUBK. Slide 13 shows that this modeling approach allows analysis of contributions to BLLs by exposure pathway and for all percentiles of the entire United States population. Slides 14 and 15 illustrate how EPA identified the maximum daily average household tap water lead concentrations that could keep BLLs below the specified values of 3.5 µg/dL and 5 µg/dL.

In response, a reviewer noted that the SHEDs model walks a hypothetical individual through exposures over time (e.g., 0 to 7 years) and that some of EPA's inputs (e.g., soil/dust ingestion rates) are based on probability distributions. The reviewer requested EPA clarification on the number of times that the Agency randomly

drew a value from the probability distribution to represent the input parameter for a given child in the probabilistic modeling approach.

> **EPA Clarification:** The SHEDS model uses the diary data time steps to simulate exposures related to an individual's activity patterns. For each of these time steps, the model draws probabilistically from the concentration and exposure factor distributions. EPA uses a published approach to construct longitudinal exposure profiles, stringing together the different diaries over time, which are then averaged over a certain period. The SHEDs model preserves within-day variability from the diaries it uses, however, because of the IEUBK time step, EPA used a daily average from the SHEDs values. When processing IEUBK output, EPA used a 30-day averaging time.

Another reviewer noted that the IEUBK model is a long-term exposure model that requires a steady state assumption and produces long-term (typically one year) averages. The guidance requires a minimum averaging period of 90 days and at least one exposure per week. The reviewer questioned if 30-day averages from IEUBK model are appropriate to couple with the SHEDs model, which incorporates data from exposure diaries.

> **EPA Clarification:** One of the recommendations that EPA received from their previous peer review consult was to use another model that can evaluate shorter durations of exposure. EPA found that if they evaluated acute high-level exposures over the course of a few days, as opposed to time-weighted average exposure, they would end up with the same average BLL over the course of a month. This provided additional confidence for using the more steady-state IEUBK model. EPA also mentioned that concentration spikes are difficult to interpret, but that long-term averages can be associated with health endpoints such as IQ loss.

2.2 Public Statements

Connery then facilitated a public comment session, in which observers who had signed up to do so made oral statements. Four observers provided comments, as summarized below (see Appendix G for their full statements): Tom Neltner (Environmental Defense Fund), Warren Friedman (U.S. Department of Housing and Urban Development), Douglas Crawford-Brown (University of Cambridge)[7], and Lindsey Jones (Texas Commission on Environmental Quality [TCEQ]).

- *Tom Neltner:* Neltner thanked EPA for their presentations and noted that this is an important outgrowth of the discussion that occurred in the Lead and Copper Rule Working Group. During that discussion, members identified the need to develop a concentration of lead in drinking water that would trigger a public health investigation. He commented that this was not an attempt to define a safe level for lead in drinking water; that level is 0 µg/L. The purpose of this household action level is to provide parents, doctors, and the public health community information so that they can make decisions for a given child. Nelter noted that the Working Group recommended that EPA evaluate the most vulnerable group (i.e., formula fed 0- to 6-month-old infants), but appreciated EPA's efforts to go beyond that suggestion.

- *Warren Friedman:* Friedman thanked EPA for the opportunity to provide public comments on the lead modeling effort and noted that the views reflected in his comments do not necessarily represent HUD's position. He acknowledged the use of the 1950 versus 1978 cut point to identify

[7] As noted in Appendix G, Dr. Crawford-Brown's attendance at this meeting was sponsored by the American Water Works Association (AWWA).

homes with likely sources of lead paint as a reasonable approach for the modeling exercises. He expressed concern with the conversion model that EPA selected to convert dust lead loading levels (µg/ft^2) into dust lead concentrations (µg/g). Friedman noted that this conversion model does not provide quantitative precision or uncertainty estimates for the coefficients of the equations. He encouraged EPA to carefully assess the effect of this uncertainty on the current modeling effort.

- *Dr. Douglas Crawford-Brown:* Dr. Crawford-Brown noted the challenge of basing a regulatory decision on lead exposures within the context of aggregate risk and a "risk cup" (i.e., how does one identify the specific exposure [e.g., air, paint, water, soil] that pushed an individual over the rim of the "risk cup"?). He mentioned that EPA has suggested developing a probability distribution for the impact of different water concentrations on BLLs in a population. This incorrectly assumes that waterborne lead is what 'pushed' an individual over the rim of the "risk cup". Dr. Crawford-Brown suggested an alternative approach whereby the entire US population is modeled, while accounting for all routes of exposure, to understand the impact on that distribution when water concentrations are lowered to a specific level. Approach 3 is the only method that allows for this type of assessment. Dr. Crawford-Brown also expressed concern with the selected biological averaging time and encouraged the panel to propose an appropriate value and assess how the model accounts for short-term fluctuations in waterborne exposures. He also suggested that the panel consider the issue of truncation and correlation in the underlying distribution of the model parameters.

- *Lindsey Jones:*[8] Jones thanked EPA for the opportunity to provide an overview of TCEQ's written comments. She encouraged the panel to guide EPA away from using the term "health-based benchmark" for the modeled output, and suggested a more accurate descriptor, such as household screening level. Jones cautioned against tying an action level to an ever-moving target, such as the 97.5th percentile of the U.S. childhood BLL distribution. She suggested that the panel focus on Approach 1, which is consistent with EPA's historical approach for assessing lead exposure, and apply the 37 µg/g and 72 µg/g geometric mean background soil and dust lead concentrations, respectively. Jones also recommended that the panel give the soil ingestion, soil/dust concentration, and outdoor air input parameters an appropriate level of scrutiny.

2.3 Reviewer Discussions

Connery then turned the meeting over to Dr. Barry Ryan, the panel chair, to begin the reviewer discussions. As shown in the agenda (Appendix D), the reviewers discussed each of the five charge questions in the order they appeared in EPA's charge to reviewers (Appendix B) and concluded the meeting with individual closing remarks. Sections 3 through 8 of this report summarize those discussions.

3. REVIEWER DISCUSSION: CHARGE QUESTION 1 (MODEL SCENARIOS)

Charge Question 1 (Model Scenarios): Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 µg/dL and 5 µg/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

[8] Connery read these comments on behalf of Ms. Jones, as Ms. Jones was attending the meeting remotely.

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years.

Reviewers expressed a variety of views on the strengths and weakness associated with modeling the three proposed life stages: 0-6 months, 1-2 years, and 0-7 years:

- *0- to 6-month age group*: All reviewers agreed that this critical age group should be included in the proposed lead modeling approaches. As one reviewer noted, due to the limited mobility of 0- to 6-month-old children, this group would not likely experience other significant exposures to lead besides tap water/formula. This creates an ideal group for evaluating lead in drinking water. Breaking this group into formula-fed and general scenarios was recognized as a strength by two reviewers. Breast milk was identified as another potential source of lead exposure, but intake of breast milk with lead levels equivalent to tap water would likely be supplemented by tap water/ formula at essentially the same level. Two reviewers acknowledged the lack of NHANES data to estimate baseline BLLs for this age group as a limitation.

- *1- to 2-year age group:* Reviewers generally agreed that the 1- to 2-year age group was suitable for the proposed lead modeling approaches. One reviewer noted other possible boundaries for this life stage (e.g., 1 year to 16 months), but agreed that the selected 1- to 2-year age group was equally justifiable. Another reviewer encouraged EPA to focus on this 1-year interval because the relative body-weight normalized water consumption is rate highest for 1- to 2-year old children, and the overarching goal of understanding the impact of the drinking water pathway on baseline exposures (i.e., non-drinking water exposures). Dietary intake of lead was identified as another potential source by another reviewer, but of lesser concern in the United States than in other countries with contaminated food supplies.

- *0- to 7-year life stage.* Several reviewers expressed various concerns with the proposed 0- to 7-year age group:
    - As one reviewer noted, exposures differ substantially over this life stage and the parameters needed to model this diverse-activity stage vary widely.
    - Another reviewer pointed out that the emphasis seems to have been put on the biological effects observed at different ages within the 0- to 7-year period, rather than on exposures. The assumption that constant ingestion variables carry through from lower to higher ages is concerning.
    - Recognizing the goal of evaluating cumulative exposure for this age group, a reviewer noted that stochastic approaches offer a better evaluation of the exposure impacts across the 0- to 7-year time period, compared to the shorter duration of early life stages that rely on measures of central tendency.
    - Several reviewers suggested that the 0- to 7-year age range be broken into smaller groups to account for behavioral changes.
    - The 2- to 4-year age group was identified by one reviewer as a critical period due to increased ingestion from soil and dust and movement to different environments (i.e., outside the home).

Please comment on whether there are additional life stages that should be considered by EPA.

A reviewer recommended that the proposed 0- to 7-year age group be divided into two shorter age ranges: 0 to 5 years (representative of children not yet enrolled in school) and 5 to 7 years (representative of

children in educational facilities). He noted that this change would support current regulatory efforts focused on lead testing in schools. Two other reviewers agreed with this point, although one noted that stochastic modeling approaches can account for the expected variability between the 0- to 5-year and 5- to 7-year age groups. These types of behavioral changes would be difficult to account for with Approaches 1 and 2.

Reviewers offered several other comments and recommendations:

- A reviewer advocated for inclusion of a 3- to 5-year age group, to represent children in preschool or day care facilities.

- Another reviewer suggested expanding the proposed age range to include early and young adolescents, for whom there is reduced soil and dust exposure and increased exposure from other sources (e.g., occupational exposures). In addition, gender-specific effects may be worth exploring as children age from early childhood through adolescence.

- A reviewer suggested extending the proposed age range to the ages of 11 and 12, based on documented health effects in the peer-reviewed literature (e.g., delayed onset of puberty) and observed behavioral/social changes.

- Reviewers recommended that EPA consider a scenario to reflect *in utero* exposures and risk to the fetus. One reviewer specifically highlighted the need to better understand maternal BLLs and maternal contributions to total lead exposures, as a starting point for the default level used in IEUBK modeling. This reviewer stressed the importance of communicating that the maternal BLLs included in the models represent women of childbearing age, and not necessarily women who are childbearing. With consensus on how to define childbearing age, NHANES data could be used to estimate a reasonable concentration at this age. Inclusion of prenatal exposures, according to one reviewer, would be a significant effort. If modeling this pathway is not possible, another reviewer noted that EPA could examine the peer-reviewed literature. A reviewer acknowledged that the IEUBK model is limited in its ability to model this life stage and suggested that EPA consider a physiologically based pharmacokinetic (PBPK) model, which would allow for examination of maternal, fetal, and infant exposures (from breast milk).

- The baseline BLL currently ascribed to mothers in IEUBK models (0.61 µg/dL) seemed low to one reviewer. Another reviewer thought that the value was reasonable, but suggested that EPA conduct a sensitivity analysis to better understand the impact of the selected baseline BLL. A third reviewer pointed out that changing limits of detection and the processes to input these values could substantially impact the starting maternal BLL.

The panel chair noted that there seemed to be agreement among reviewers on the benefit of gathering data from conception to birth and associated challenges, as well as the usefulness of partitioning the 0- to 7-year age group into two separate groups (0-5 years and 5-7 years) that account for the different exposures, environment, and social structures among children before and after they enter school. At the request of the panel, the chair asked EPA to clarify why they selected the 0- to 7-year age group.

> **EPA clarification:** EPA directed participants to page 6 of their summary report and read the definition of the proposed 0- to 7-year age group: "*This group accounts for individuals potentially being exposed to lead in drinking water throughout their childhood to age 7. Additionally, this age group represents cumulative exposure during the period over which lead exposure is estimated to have the greatest*

response in regard to changes in per unit IQ." EPA clarified that they are asking the panel to review the scientific methodologies to help inform a health-based benchmark or household action level in the context of a potential regulatory proposal, for which they must estimate costs and benefits. EPA acknowledged that an increase in BLL is not an adverse health outcome that has a quantifiable benefit if avoided, but that IQ decrements are. The 0- to 7-year age range may therefore be informative for evaluating a household action level, as well as additional analyses on impacts of avoided adverse health outcomes.

EPA was then asked to further define the metric that the Agency proposes sharing with policy makers for the 0- to 7-year age group (e.g., average exposure, peak exposure).

EPA clarification: EPA stated that if the Agency were to quantify the benefits of avoided lead exposure for life stages from 0 to 7 years old, they would use the modeling approaches described in the draft review document to predict IQ decrements that would be avoided because of the treatment technique requirements of a proposed LCR.

In response, one reviewer mentioned that a 1 µg/dL increase in blood lead resulting in a 1-unit decrement of IQ was used to derive a public health goal in California. Another reviewer noted that it will be difficult for EPA to determine the proper index to relate to IQ. To do so, added a third reviewer, EPA will need to understand the age range and summary statistic that is best supported by epidemiologic research.

When asked by the chair whether the 0- to 7-year age range was appropriate for this use, reviewers acknowledged the need for clarifying the goal of this peer review and how the modeling outputs will be used. Context and semantics were identified as critical parts of this discussion. As an example, one reviewer noted the different interpretations of a household notification value and health-based benchmark. Two reviewers expressed a preference for the term "reference value."

Please also comment on the strengths and weaknesses of the modeling scenarios conducted (i.e., exposures scenarios for drinking water only and all pathways that target the BLL 3.5 µg/dL and 5 µg/dL at several upper tail percentiles).

Reviewers generally agreed that EPA has framed the scenarios to provide useful information from many different perspectives. Given that the goal of this exercise is to understand the contribution of drinking water exposures above and beyond non-drinking water exposures, one reviewer specifically commented on the merit of including model runs that first look at non-drinking water exposures only, and then with the addition of the drinking water pathway. Two reviewers noted the utility of looking at drinking water exposures alone, as a way to understand the relative source contribution of that pathway.

Several reviewers commented on use of upper percentiles.

- The proposed modeling approaches evaluate the contribution of environmental exposures to elevated BLLs, noted one reviewer. This means that a 95th or 97.5th percentile cannot be interpreted as a threshold of health effects (i.e., it cannot be tied to a certain cognitive impairment). EPA needs to be very clear in their terminology, particularly in defining modeling outputs that are based on a population-level estimates.

- A reviewer expressed concern with using an upper end percentile of the national data in the proposed modeling approaches, referencing areas in the country with poor lead poisoning prevention programs. The reviewer noted that the upper end of the national distribution of BLLs is most likely impacted by sources other than water (e.g., leaded paint). A modeling exercise based on lead in drinking water that is driven by the tails of a national distribution of BLL will have minimal

impact in these areas. This reviewer suggested using the geometric mean or median as an alternative metric.

- A reviewer commented that looking at percentiles of high BLLs means that we are focusing on high-risk areas (e.g., where many homes have lead service lines), for which there is little to no information in the United States. The upper percentiles represent a subgroup of older houses with high concentrations of lead in drinking water, variable concentrations, and where there likely are other significant sources of lead exposure. This reviewer struggled to understand the interpretation of the 95th or 97.5th percentile when used with the NHANES data, and questioned how to draw inferences on what will happen with water by evaluating the tail end of this distribution.

- A reviewer stressed the importance of clearly defining the correct interpretation of a percentile of a probability distribution of BLLs. Percentiles from the proposed modeling approaches can be interpreted to represent either the fraction of the population that is expected to have a BLL less than or equal to a specified BLL, or the probability that an individual selected at random will have a BLL less than or equal to a specified BLL. EPA was encouraged to provide a very clear explanation of what the percentile is intended to represent so that reviewers can fully understand what the modeling scenarios represent.

Following this discussion, EPA offered clarification on the regulatory context in which the proposed modeling approaches were developed.

> **EPA Clarification:** EPA noted that they are not developing a health-based benchmark solely to inform corrosion control treatment. The value could also be used to guide other actions that could be taken system-wide or at an individual site, such as public education; outreach to consumers to let them know actions they can take to reduce exposure to lead in drinking water; prioritization of lead service line replacement; and as suggested by NDWAC, triggering of notification to the household, state drinking water program, and local public health authority. These potential requirements would be imposed on public water systems. For lead service line replacement, potential requirements apply only to the part of the service line that that is owned by the water system.

One reviewer responded by acknowledging the importance of the selected risk metric (e.g., an absolute BLL, delta BLL). As the contribution from baseline increases, the health-based benchmark will decrease for risk metrics that are based on the absolute BLL. But for risk metrics based on delta BLL, the health-based benchmark will be less sensitive to the choice of summary statistic used to represent baseline. Only when water dominates the total exposure can you expect this regulation to have a large influence, and that influence will be more easily measured with delta BLL than an absolute BLL (e.g., 3.5 µg/dL, 5 µg/dL). Another reviewer agreed and noted that different metrics can have different regulatory consequences.

A reviewer commented on the overall goal of the proposed modeling approaches, whereby EPA is trying to understand what levels of lead through normal processes in the distribution system will lead to elevated BLLs. These elevations usually derive from stagnating water that comes as a bolus source of lead contribution to these children, which is not being evaluated directly in the proposed modeling approaches. Given how these data will be used to inform lead policy, this reviewer encouraged EPA to make sure that the model being developed is fit for its intended purpose.

As an alternative approach that would address some of the challenges associated with modeling these exposures (e.g., soil and dust ingestion rates, correlation structure between inputs, and representativeness of sampling data to national summary statistics), one reviewer suggested that EPA begin by developing non-drinking water exposure scenarios that reproduce the NHANES summary statistics and then building in the

drinking water scenario. Another reviewer agreed with the utility of this approach and recommended looking at the distribution of NHANES BLLs to identify at-risk populations, and then modeling different water scenarios to understand the environmental contributions that led to the observed BLLs. This reviewer also noted that there may be other sources of BLL monitoring data to support these types of modeling efforts (e.g., Massachusetts childhood lead monitoring surveillance data).

Please identify additional scenarios that would add utility.

Six reviewers suggested additional model scenarios that are stratified by geographic region. These scenarios would account for the important variability observed between urban and rural areas, and across climatic regions. Specific comments and recommendations are as follows:

- A reviewer made the point that "Similarly exposed populations" are the premise of the proposed modeling approaches. National modeling of lead exposures and BLLs is not appropriate; these models will be diluted by the millions of children without lead exposures. As such, this reviewer suggested stratifying models with a focus on areas of high exposure, rather than trying to replicate the entire distribution of the United States.

- Three reviewers recommended that EPA use the NHANES database to identify communities with elevated BLLs and then evaluate the contribution of lead from local environmental conditions and water systems. One of these reviewers suggested stratifying on geographic areas that represent low, medium, and high exposure conditions. Another reviewer suggested stratifying by areas where there is known to be a high percentage of homes with lead services lines.

- One reviewer noted that EPA's ability to use the coupled SHEDs and IEUBK modeling approach to reproduce the national distribution of BLLs provides confidence that the approach can be applied to more heavily exposed populations, if the proper inputs are available.

Following this discussion, reviewers requested that the chair ask Warren Friedman, the public commenter affiliated with the Housing and Urban Development (HUD), if housing data were available to help guide these efforts and to what extent EPA could pair any available housing data with BLLs documented through NHANES.

> **Observer (Warren Friedman) Clarification:** HUD has shared data from its American Healthy Homes survey and National Survey of Lead and Allergens in Housing with EPA. HUD is willing to share any other data that would be useful, if suitable personal identifiable information protections can be maintained. Regarding the ability to pair housing data with BLL data from NHANES, HUD referenced an example from a paper by Katherine A. Aherns (CDC), Barbara A. Haley (HUD), and colleagues[9]. Researchers found that children living in assisted housing had approximately 20% lower BLLs than comparable children living without housing assistance, when analyses were controlled for socioeconomic and geographic factors. In addition, children in assisted housing had a lower prevalence of BLLs greater than 3 µg/dL.

Reviewers suggested additional modeling scenarios that account for the temporal variability in concentrations and drinking water ingestion rates, and made several specific comments and recommendations:

- A reviewer noted that different water lead concentrations are measured within distribution systems and through time, due to factors such as time of stagnation and temperature. There are also

[9] Aherns, K.A., B.A. Haley, L.M. Rossen, and P.C. Lloyd. Housing assistance and blood lead levels: children in the United States, 2005-2012. American Journal of Public Health 2016; 106(11): 2059-2056.

occasional spikes in lead concentrations following extreme events. This reviewer stressed the importance of accounting for these types of extreme concentrations and expressed concern that the proposed modeling approaches do so. If the models are to be used to inform policy for lead service lines, they should account for extreme concentrations.

- Two reviewers pointed out that Important biological differences occur during these extreme events; large acute bolus doses of lead affect the body differently than chronic exposures to lower concentrations.

- A reviewer suggested that EPA consider the transient nature of lead in drinking water and develop standards that can accommodate shorter time windows (e.g., a 0- to 3-day notification level, a 10-day subchronic/chronic notification level), in addition to a long-term chronic value. The proposed modeling approaches should account for duration of exposure.

- A reviewer commented that Monte-Carlo simulations are one approach to account for the temporal variability in exposures to lead in drinking water.

- Another reviewer pointed out that increases in lead sampling in schools and in some homes within distribution systems provide data that could be used to explore these questions.

- A reviewer noted that several recent publications have evaluated these issues with different modeling frameworks (e.g., International Commission for Radiation Protection [ICRP] Age-Specific Biokinetic Model for Lead developed by Leggett and colleagues) and highlighted several concerns from this literature[10], in support of the suggestion to explore the impact of temporal variability:
    - The 1-year averaging time model input may underestimate long-term steady state BLL concentrations if there are sustained periods of elevated exposure.
    - The magnitude of this underestimation depends on the relative contribution of baseline exposures (i.e., non-drinking water exposures).

4. REVIEWER DISCUSSION: CHARGE QUESTION 2 (MODEL INPUTS)

Charge Question 2 (Model Inputs): Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort and on soil/dust ingestion rates and other key factors.

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS modeling approaches. Please

[10] Lorenzana, R.M, R. Troast, J.M. Klotzbach, M.H. Follansbee, and G. Diamond. 2005. Issues related to time averaging of exposures to lead. Risk Anal. 25(1):169-178.

McLanahan, E., L. Wilder, K. Scruton, K. Bradham, and R. Worley. 2016. Evaluating the All-Ages Lead Model Using Site-Specific Data: Approaches and Challenges. Presented at Society of Toxicology Annual Meeting. March 13-17.

California EPA. 2016. Comparison of All Ages Model Version 4 with Leadspread 8 in Evaluation of Lead Exposure at California Hazardous Waste Sites. Poster by K. Gettmann, L. Nakayama Wong, and M. Wade. 2016. Presented at Society of Toxicology Annual Meeting. March 13-17, New Orleans, LA.

identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates.

Approaches 1 and 2 rely on point estimates, while Approach 3 applies a combination of point estimates and probability distributions. A reviewer began the discussion by noting that IEUBK models with input values that represent measures of central tendency from point estimates do not necessarily produce corresponding outputs that represent measures of central tendencies from distributions. Based on this logic, the reviewer stressed that although Approaches 1 and 2 provide valuable insight, they do not produce results that are generalizable to the larger population. He expressed a preference for Approach 3, which incorporates a distributional application of the data, but with reservations on how correlated variables were addressed (e.g., the correlation between soil and dust concentrations at the tail end of a distribution). He recommended that EPA provide detailed information on the inputs, assumptions, correlations, and data gaps incorporated into the various proposed modeling approaches.

Another reviewer agreed with the need to consider correlation. This reviewer also expressed a preference for Approach 3, noting that Approaches 1 and 2, which rely solely on point estimates, do not account for underlying variability. As an alternative approach, she recommended that EPA consider coupling the SHEDs model with a PBPK model, which would ultimately account for variability in biokinetics. This reviewer also suggested that point estimates for the IEUBK model be sampled from a distribution using a PBPK modeling framework, in combination with Monte Carlo analysis.

A reviewer suggested that EPA develop a more sophisticated soil and dust concentration distribution for use in Approach 3, rather than relying solely on point estimates. This could be done by stratifying the database to look at different parts of the county, particularly areas with highly exposed populations.

> **EPA Clarification:** EPA clarified that they did not use point estimates for soil and dust lead concentrations in Approach 3 and referred the audience to Slide 9 of their introductory presentation, which summarized the soil and dust lead distributional data used from the HUD American Healthy Homes Survey. These empirical data included 223 dust samples collected before 1950, 908 dust samples collected after 1950, 193 soil samples collected before 1950, and 749 soil samples collected after 1950.

Two reviewers encouraged EPA to explore other databases to improve exposure and BLL estimates:

- One mentioned the utility of HUD's American Healthy Homes survey. This database could be further explored to better understand the distribution of lead levels among homes constructed prior to 1950.

- The other noted that she recently shared profile sampling data of lead service lines in the United States, as well as a large body of data from Canada, with EPA. She acknowledged that the proposed modeling approaches are largely back calculations, but encouraged EPA to consider adding some of these data to the front end in order to expand the interpretation of the developed approaches.

Four reviewers commented on the need for EPA to acknowledge uncertainties associated with including non-detect results in the modeling exercises:

- As concentrations of lead in drinking water and blood continue to decrease, noted one reviewer, it is critical to understand how non-detect values and the process by which they are imputed into a dataset can impact modeling inputs and outputs. Non-detect values may bias the estimated geometric standard deviations (GSD) downward.

- Another reviewer commented that non-detects are not imputed in a consistent fashion. He encouraged EPA to document these types of methods and data gaps in their discussion of modeling uncertainties.

- A third reviewer described his work following children at Bunker Hill over a 30-year period, and the effect that decreasing detection limits had on the downward trends observed for measured BLLs.

- The fourth reviewer pointed out that the way that detection limits are imputed can have a large effect on estimated risks. As such, he encouraged EPA to not underestimate the effect of non-detects on predicted BLLs.

A reviewer suggested that, when data are sparse, EPA consider using analogous information as a surrogate. For example, the 0- to 6-month intake values, which are based on a very limited dataset (i.e., seven results), could instead be based on documented rates of breastfeeding.

Several reviewers discussed alternative approaches:

- A reviewer acknowledged the excellent work that went into developing the proposed modeling approaches, but suggested that EPA consider a simpler approach for drinking water. She questioned the use of complex models when evaluating drinking water exposures for an age group for which there are no BLL data and very limited information on consumption rates (i.e., the 0- to 6-month age group). As an alternative approach, she recommended simplified calculations like those used in the European Union.

- Another reviewer agreed with the value of considering simpler modeling approaches, especially given the sparse data for the 0- to 6-month-old scenario. He suggested relying on the integrated metric of multiple exposure pathways that is available through measured BLLs as a basis for understanding the relative source contribution of water compared to non-water exposure pathways. If the water pathway and key input parameters (e.g., water ingestion rates for the different age groups) could be modeled precisely, all other pathways could be represented with a simple empirically grounded method: the use of NHANES data. The reviewer acknowledged that this approach doesn't provide all the benefits of a probabilistic method, but given EPA's goal of understanding appropriate trigger levels for action, he argued that there is no need to evaluate the relative contribution of air, soil, and dust. The proposed modeling approaches could be simplified with a point estimate method that includes a "lumping" term to account for all non-drinking water pathways and relies on the GSD.[11] Limitations of the GSD could be explored with sensitivity analyses.
    - In response to this suggestion, a reviewer noted the benefits of comprehensive mechanistic tools for generating and testing hypotheses in the absence of data. These models are also valuable for identifying data gaps. In most cases, a model is most useful as a hypothesis generator rather than as a predictive tool. The reviewer commented that a simpler model which "lumps" exposures together may hide key information.
    - The previously mentioned reviewer responded by acknowledging the utility of mechanistic models when evaluating specific sites and needing to partition source contributions, but maintained that this is not the goal of the modeling approaches proposed by EPA. Since all the proposed modeling frameworks ground truth results based on their comparison to

[11] Additional details can be found in Dr. Philip Goodrum's post-meeting comments, provided in Appendix H.

measured BLLs, the reviewer questioned why EPA does not use the BLL data directly. Although his suggested simpler approach removes the ability to test hypotheses and identify data gaps, it allows EPA to establish a better model prediction of BLLs if action were taken (e.g., the impact would be on BLLs if lead concentrations in drinking water were controlled).
    - A third reviewer noted the utility of both approaches; the simplistic model potentially offering a way to identify the impact of drinking water exposures on top of baseline nondrinking water exposures, and the more complex approaches proposed by EPA offering useful exploratory research tools.

- A reviewer encouraged EPA to consider these suggested alternative approaches as additional approaches, rather than replacements for what has already been development.

During these discussions, a reviewer noted that EPA's report says that their analyses do not represent high-end exposures. However, she believed that in some cases they did. For example, some input parameters (e.g., outdoor air and soil concentrations) were based on the higher end of the exposure range.

Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort and on soil/dust ingestion rates and other key factors.

To compare the different modeling approaches side by side, EPA had to develop inputs (i.e., soil/dust ingestion rates and water consumption rates) that could be used across all three approaches. The point estimates for the first two approaches were changed from default IEUBK values to align with the diary-based information that goes into the SHEDs part of the third modeling approach. One reviewer expressed concern with EPA's decision to change the statistical measure of central tendency from an arithmetic mean to a geometric mean, based on the observation that geometric means better predicted BLLs from NHANES. The reviewer questioned how a difference between NHANES and BLLs could be attributed to a single exposure variable. In addition, the reviewer noted that the use of geometric means is not consistent with historical approaches of IEUBK modeling and will result in lower estimates of exposure from the drinking water pathway.

A similar concern was expressed by another reviewer, who noted that the values used in the proposed modeling approaches are inconsistent with guidance, recommendations, and the Agency's regulatory history. This reviewer questioned the utility of demonstrating that results from one model are consistent with another, if one of those models is not being used as it was designed (e.g., the IEUBK model was not designed to accept inputs based on geometric means). This reviewer also noted that the IEUBK model assumes a single exposed population and therefore, may not be appropriate to compare to the SHEDs model. The SHEDs model incorporates a national database with much larger variance than the IEUBK was designed to accommodate. The use of geometric means will result in lower predicted exposures, which is not appropriate unless EPA also changes the GSD to capture higher concentrations. In addition, the national database likely underestimates exposure factors.

Four other reviewers commented on differences in default IEUBK values and those included in the proposed modeling approaches. One of these reviewers questioned if the assumptions that are the basis of the IEUBK model were consistent with the proposed modeling approaches.

The default GSD of 1.6 that is typically used when applying the IEUBK model was designed to represent all aspects of uncertainty and variability, except for variability in concentrations across different households. A reviewer recognized that EPA had changed this for Approach 3, to represent variability in BLLs on a national scale by using a GSD that accounts for variability in exposure concentrations. This reviewer was concerned that a GSD of 1.6 may be too low, given that EPA is now including variability in the concentration term.

Another reviewer made the point that arithmetic means and geometric means were selected based on whether data were found to be "highly variable" or "lognormally distributed." This reviewer encouraged EPA to examine data defined as "highly variable" for sources of heterogeneity and to ensure that the data represent one distinct population.

Several reviewers commented on the soil/dust ingestion rates:

- A reviewer expressed concern with how EPA selected soil/dust ingestion rates by fitting the IEUBK to national BLL distributions and modifying the input parameters.

- Two reviewers identified the lack of variability across age-specific soil/dust ingestion rates as a major concern.

- One reviewer commented on EPA's decision to rely on the soil/dust ingestion rates published in Özkaynak et al. (2011)[12] rather than those estimated by von Lindern et al. (2016)[13]. The reviewer cited EPA's preference for using values from Özkaynak et al. (2011) because that reference offered probability distributions for each of the modeled age groups. However, the von Lindern et al. (2016) publication also estimated age-group specific probability distributions, which are available in their published supplement. The reviewer advocated for EPA to use the von Lindern et al. (2016) point estimates and probability distributions. This approach relied on the IEUBK model to adjust soil and dust ingestion rates to fit measured BLLs. The reviewer noted that this approach is scientifically sound and builds on methodology commonly used in human health risk assessment.
    - As a follow-up to this discussion, the panel asked EPA to clarify how they conducted the sensitivity analysis described in the draft Zartarian et al. (2017) manuscript[14] using results from von Lindern et al. (2016).

      EPA Clarification: EPA confirmed that they used the distributional data from the von Lindern et al. (2016) publication in their sensitivity analyses. More specifically, EPA used the published percentiles, geometric mean, and GSD for the 1-year-old age group to simulate the whole distribution. EPA only evaluated the 1-year-old scenario because this was the age group for which they observed the largest difference between their estimates and those reported by von Lindern et al. (2016). The first sensitivity analysis used a distribution with a central value of 100 mg/day. This value was scaled up proportionally (by multiplying the ratio of 100/60) from the distribution with an average of approximately 60 mg/day, as generated in SHEDS-Multimedia based on the Ozkaynak et al. (2011) methodology.

      When asked how this related to the geometric value of 26.6 mg/day, EPA noted that 26.6 mg/day is the geometric mean of soil/dust ingestion rates generated by the SHEDS approach (using data from Özkaynak et al. [2011]); however, Approach 3 does not use this geometric mean but instead uses the distribution generated by SHEDs.

[12] Özkaynak, H., J. Xue, V.G. Zartarian, G. Glen, and L. Smith. 2011. Modeled estimates of soil and dust ingestion rates for children. Risk Anal. 31(4):592−608.

[13] von Lindern, I., S. Spalinger, M.L. Stifelman, L.W. Stanek, and C. Bartrem. 2016. Estimating children's soil/dust ingestion rates through retrospective analyses of blood lead biomonitoring from the Bunker Hill Superfund Site in Idaho. Environ. Health Perspect. 124(9):1462−1470. DOI:44 10.1289/ehp.1510144.

[14] Zartarian, V., J. Xue, R. Tornero-Velez, and J. Brown. 2017. Children's lead exposure: a multimedia modeling analysis to guide public health decision making. Environ. Health. Persp. Manuscript Draft.

When asked how EPA input data from von Lindern et al. (2016) for the sensitivity analysis, EPA noted that they fit an empirical distribution generated by the percentiles shown in table S1 of supplemental materials published with the von Lindern paper.

A reviewer responded by requesting that EPA explain this more thoroughly in their report and look more closely at the other age groups evaluated in the von Lindern et al. (2016) reference.

Several reviewers commented on the water consumption rates based on NHANES data:

- Four reviewers questioned why EPA did not consider the water consumption rates provided in EPA's Exposure Factors Handbook. One reviewer specifically noted that the water consumption rate used for children is approximately one-third lower than the IEUBK default recommendation
- According to one reviewer, the water consumption rates used for formula-fed infants and 1-year old children is particularly low.
- A reviewer also commented on the variability of soil/dust lead concentrations and how the use of point values for these parameters ignores that variability. The reviewer acknowledged the challenges with soil/dust media and suggested that EPA consider spending more time evaluating the soil and dust concentration term. In particular, the reviewer stressed the importance of partitioning the relative source contributions from exposures within the home, yard, play areas, neighborhood, and larger community. EPA has employed techniques in the past that can be used in sensitivity analyses to look at the impact of those concentration variables.

5. REVIEWER DISCUSSION: CHARGE QUESTION 3 (MODELING APPROACHES)

Charge Question 3 (Modeling Approaches): Please compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

A reviewer started the discussion by noting that the proposed modeling approaches include three main components that need to be considered: modeling constructs, inputs, and risk metrics. He highlighted the importance of accounting for the underlying correlation structure between the time steps in Approach 3, noting that failure to do so may influence the overall variability in modeled outputs. He recommended that a sensitivity analysis be conducted to explore the time steps and correlation structures.

A reviewer noted that diary models (e.g., SHEDs) typically assume that behavior remains constant throughout the modeled period. This is particularly concerning for the 0- to 7-year age group scenario, for which behaviors are undoubtedly changing. This reviewer questioned how EPA accounted for variability over this longer trajectory and suggested additional discussion in the final report. He requested clarification from

EPA regarding how time step autocorrelation was accounted for in Approach 3. Another reviewer noted that the time step correlation structure likely varies with age

EPA Clarification: EPA did not simulate each life stage within the 0- 7-year age group for Approach 3; life stages within the 0- to 7-year age range were evaluated as a group.

A reviewer noted that this is different than the standard application of SHEDs and encouraged EPA to clarify this point in their final report.

When asked by the chair to compare and contrast the three modeling approaches, reviewers generally noted that all approaches had their merits and provided different but complementary information. Specific comments were as follows:

- One reviewer commented that Approach 2 provided more useful and practical information than Approach 1. Another reviewer agreed with this point, but expressed a preference for Approach 3, which looks at the entire population.

- A reviewer encouraged EPA to explore and evaluate how the IEUBK model and its modified version (Approach 3) performs when exposure ends and blood lead decreases.

- A reviewer acknowledged the historic utility of Approach 1 as an enforcement tool, but questioned how the public will interpret the modeled output. Approach 2 provides useful information on how BLLs change, which can be extended to understand changes in BLLs at any point of the distribution. As for Approach 3, the reviewer questioned the public health significance of the modeled output. The output estimates the percentage of the United States population that is over a certain threshold BLL, but does not help public health practitioners understand measured concentrations of lead in drinking water.

- Another reviewer commented on the importance of grounding modeling assessments with a public health-based interpretation. The reviewer encouraged EPA to further explore whether individuals with high BLLs are the same individuals drinking water with high lead concentrations, with a suggestion to look more closely at those children with high BLLs. The reviewer recommended that EPA consider the alternative approach of developing a “lumping term” that would define a child at the upper end of the distribution, and then determine the additional contribution of water to that child that would require notification to a local health agent.

- A reviewer noted that Approach 1 has been historically useful for utilities, but that Approach 2 provides more practical output. The reviewer encouraged EPA to provide more background on the chosen delta values of 0.5 µg/dL and 1 µg/dL in Approach 2. Approach 3 could be improved by incorporating data on measured lead concentrations in water. The reviewer expressed general concern with how the models were fit to NHANES BLL data and how different the modeled outputs were across the three approaches. Considering model uncertainties, the reviewer cautioned EPA in defining these modeled values as health-based benchmarks. The reviewer also noted that the modeled levels could have serious consequences in terms of corrosion control and tolerable levels in lead service lines. It is important that EPA ensures that the mean computed levels are reasonable, since they transfer in practice to very high concentrations in lead service lines.

- While the proposed uses of the IEUBK model may provide valuable information, one reviewer questioned if the modeled outputs were relevant to the national distribution of BLLs. The reviewer also questioned whether the proposed modeling approaches could be applied to the tail ends of the distribution with available data. Of the three proposed modeling approaches, this reviewer was most comfortable with Approach 3. This is largely because Approaches 1 and 2 apply the IEUBK model in a different manner than it was originally designed for.

- One reviewer acknowledged the utility of health metrics based on probabilities and point estimates, but expressed a preference for probability statements. These can be challenging to communicate to the public, but provide valuable information on what to expect in terms of a BLL distribution if the exposure profile changes for a group of individuals.

- Two reviewers pointed out that the geometric mean could be shifted by simply changing detection limits, and encouraged EPA to explore the impact of imputed non-detect values from their input data sources on the modeled outputs.

- Three reviewers noted the importance of understanding how well the models addressed the 0- to 6-month population. One reviewer suggested that EPA focus on the modeling approach that provides the best estimate for this age group.

Several reviewers commented on the challenges of risk communication, particularly when describing percentiles of a distribution or the probability of exceeding a certain threshold value:

- One reviewer mentioned his prior experience communicating measured concentrations of lead in water to local communities. It would be difficult for him to explain the implications of a 1 or 5 percent change in the distribution of BLLs to the public. The reviewer suggested that EPA be very clear on the interpretation of the metric that is used.

- Another reviewer questioned whether concepts from medicine (e.g., when physicians prescribe medication to an individual and describe the probability that it will work) could be applied in this discussion of risk communication.

- A reviewer questioned how modeled outputs that predict changes in BLLs would be interpreted. For example, a shift in BLLs from 1 µg/dL to 2 µg/dL would likely be interpreted with the same level of concern as a shift from 6 µg/dL to 7 µg/dL.

When asked by the panel chair to comment on which model seemed most appropriate, reviewers responded as follows:

- One reviewer highlighted the main advantage of the SHEDs-IEUBK construct as the ability to represent a risk metric that incorporates variability in the concentration term. However, the reviewer questioned whether that level of complexity is necessary for the 0- to 6-month age group. As an alternative approach, a simple lumping term could be used to estimate variance for this population, whose aggregate exposure is likely driven by drinking water. The reviewer concluded that the advantages of the IEUBK-SHEDs approach do not outweigh the uncertainties. The reviewer suggested that EPA use Approach 1 or 2, or the alternative approach whereby non-drinking water exposures are represented as a single pathway.

- Another reviewer directed the panel to slide 15 from EPA's introductory presentation (Appendix E), which shows a table of lead concentrations in household tap water that would keep BLLs below certain thresholds. The reviewer pointed out that these preliminary results could be interpreted as evidence that the current drinking water standard needs to be lowered.

- The real utility of these models is for the general population and not those with high exposures, according to one reviewer. If EPA wants to expand this interpretation, the reviewer suggested, the Agency should look at vulnerable high-risk populations and account for biological variability.
    - Two reviewers responded to this comment by noting that the IEUBK model does account for biological variability.
    - Another review commented that many of the biological variables in IEUBK are fixed. A fully vetted PBPK model, where all physiological and biochemical variables are amenable to change, would better quantify the biological variability. In the meantime, IEUBK is a useful model, however, the reviewer questioned whether the modeled outputs are being over-interpreted with the proposed modeling approaches.
    - A reviewer agreed that it would be beneficial to someday have a fully mechanistic model that allows users to examine predictions that account for variability and uncertainty in exposure, uptake, and kinetics, while being grounded in empirical data. The SHEDs model is a first step at building the front end of this type of mechanistic model. The reviewer appreciated the goal of forward thinking, but disagreed with criticism of the IEUBK model based on its black box kinetic features.
    - A reviewer questioned the appropriateness of using IEUBK to explain the BLL distribution of the United States, and suggested the model be used in stratified layers. The reviewer also mentioned that IEUBK is not very applicable to the 0- to 6-month age group.

Discussion of Charge Question 3 continued on the second day. Before discussion began, EPA offered the following clarification relevant to points reviewers had made during their discussions on the first day of the meeting.

> **EPA Clarification**: EPA acknowledged reviewers' concerns with how the Agency had conducted the model evaluation for Approach 3 and how the Agency had accounted for the spatial and temporal variability of lead in drinking water. With respect to the Approach 3 evaluation, EPA directed the reviewers to slide 8 from their introductory presentation (Appendix E) and then described their iterative model evaluation process. At each step where EPA received external feedback on improvements for Approach 3, comments were incorporated and modeled outputs were compared to NHANES BLL data to estimate relative error. With respect to variability, EPA then referred panelists to the Supplement of the Zartarian et al. (2017) paper for information on the water data the Agency used to account for some of the variability in drinking water. EPA used an empirical data distribution from EPA Office of Water's Second Six-Year Review National Compliance Monitoring dataset. These data were requested through an Information Collection Request from all states and primacy entities to voluntarily submit their Safe Drinking Water Act compliance monitoring data collected between 1998 and 2005 for the LCR. These data represent the national occurrence of regulated contaminants in public water systems. Summary statistics are available in the Supplement.

One reviewer responded by encouraging EPA to provide this information in their report, along with a graph of the distribution. Another reviewer asked for EPA clarification on the extent to which the Agency had evaluated the generalizability of those data to households within the sampled distribution systems.

> **EPA Clarification:** EPA noted that sampling under the Lead and Copper rule is not designed to assess the mean exposure concentration; rather, it is biased upwards towards identifying high levels of lead, due to the requirement to sample at sites most likely to have lead in drinking water (e.g., homes with lead service lines or leaded plumbing). For evaluation purposes, these data may represent a greater concentration of lead in drinking water than the average exposure of individuals in a given community. However, these data are the best available nationally representative dataset.

A reviewer asked for EPA clarification on how many states shared these data and for clarification on the Agency's statement that the first drawn sample from a household tap represents a high-end estimate of mean exposure.

> **EPA Clarification**: EPA noted that this dataset includes compliance data from 45 states. The LCR sampling protocol requires that water systems (or consumers who have been provided sampling instructions) collect 1-liter first draw samples after a 6-hour stagnation period. These results may therefore represent greater concentrations of lead than might occur over the course of a day when water is flowing due to normal household uses. EPA does not have a precise estimate of the degree to which this represents a higher concentration.

A reviewer asked for EPA clarification regarding how they used these distributional water data in simulations that compared predicted BLL distributions to NHANES BLLs. More specifically, the reviewer asked for clarification on how frequently a random value was drawn from the concentration term for each child.

> **EPA Clarification:** EPA used four random draws for each child for a given 30-day average. This decision was made to account for inter-personal variability.

The reviewer acknowledged that there is uncertainty with how to represent variability within a given household. EPA represented this variability through a discrete set of random draws from a national distribution. EPA could also use a single draw, this reviewer suggested, with the understanding that this draw represents a child's average over 30 days. Another reviewer noted that EPA did not draw random samples of lead concentrations for dust and paint, but instead included a stratification based on the age of housing. The reviewer asked for clarification regarding whether EPA had considered a similar stratification for water.

> **EPA Clarification:** This information was not available.

EPA then requested clarification from the panel on two points. First, given reviewers' concerns about the spatial and temporal variability of lead in drinking water, EPA requested more details about this concern and any suggestions for how to consider the variability in drinking water. Second, the Agency requested additional details on the proposed alternative approach mentioned by one of the reviewers. Regarding the first point, reviewers offered the following comments:

- EPA's simulation randomly draws from a distribution of water concentrations that represents a national average. A reviewer commented that every household is intended to be a random snapshot of the entire distribution. It would be better to assume that some children will be consistently exposed to lower concentrations. There will be greater consistency within a household than across households, over a 30-day time window.

- A reviewer questioned if EPA could take a random draw from the distribution and use that number with some degree of autocorrelation.

- A reviewer highlighted the lack of information on lead levels at the tap and encouraged EPA to look more closely at how they assign concentrations to individuals within a given distribution. The reviewer stressed the need to fully understand fate and transport in distribution systems before trying to understand risk to the children being modeling.

- A reviewer suggested mining existing databases to better understand the variability and frequency of extreme values. This reviewer encouraged EPA to look at the profiling data that was recently developed and transferred to EPA's Office of Water for further insight on how to quantify variability in the proposed modeling approaches

- A reviewer expressed the importance of understanding this variability for the concentration term used in the SHEDs model, but also in the context of the IEUBK model. Additional lead exposure for a child with a high BLL won't result in measurable increases to their BLL, but instead uptake by their bones. It is important to understand these types of acute high-level exposures among communities with high BLLs. Another reviewer mentioned that there have been efforts to represent short-term variability in exposures to lead and how that translates into predicted steady state long-term changes in BLLs.

- A reviewer noted that water concentrations of lead vary from both normal and non-normal operations. While there is limited information on variability related to non-normal operations (e.g., water quality changes and physical disruptions/disturbance events), available data demonstrate the very acute nature of these transient periods of contamination. The reviewer encouraged EPA to consider high lead concentration events in their risk analyses. The reviewer also encouraged EPA to evaluate areas with a preponderance of lead service lines and asked EPA to qualify the number of sampled houses with lead service lines. Two reviewers suggested that EPA consider different scenarios to account for this type of variability.

  EPA Clarification: For systems with lead service lines, the sampling protocol requires that 50 percent of their samples be collected from homes with a lead service line. The other tiering criteria use the age of plumbing. EPA does not require the water systems to report information on the age of houses or whether samples were collected from a home with lead service lines. However, there is anecdotal information that can be used to identify areas with the greatest preponderance of lead service lines. Considering other reviewer comments, EPA also clarified that samples for lead and copper, unlike all other drinking water regulations, are collected from household taps.

- A reviewer noted the importance of understanding whether measured concentrations at the tap in homes with lead service lines retreat to a level that is appreciably different after the first draw. The reviewer expressed uncertainty regarding whether the distribution of those household data would be the same as that of the 50,000 public water systems. The upper end of the public water system distribution may be more representative of household levels and could therefore be sampled more frequently in the SHEDs data.

In response to EPA's request for clarification on the rationale and mechanics for the alternative proposed approach, reviewers made the following remarks:

- According to the reviewer who proposed the approach, this alternative method is straightforward, simple, and consistent with some of the steps used to ground truth the SHEDs-IEUBK model (i.e., to

compare predicted BLLs from the modeling exercise to the NHANES BLL distribution). The idea is based on the premise that NHANES BLL data are an integrated measure of lead exposure through time and across pathways that can be used to represent non-drinking water pathways and associated variability. This offers a simplified approach to then evaluate the impact of adding in the drinking water pathway. The reviewer noted that there may be some double counting because water is presumably included in the baseline NHANES distribution. The reviewer pointed out that this method falls in between Approaches 1 and 2 and bypasses a lot of the uncertainty that goes into representing the concentration and ingestion rate terms for soil/dust by going straight to a lumping term (i.e., blood lead). Adding drinking water to this alternative pathway provides indication of how the BLL distribution might change when water is added to different scenarios. The reviewer noted that he would expand on this in his post-meeting comments.[15]

- Three other reviewers voiced support for this alternative approach as an addition and not as a replacement of the other proposed modeling approaches. One noted the utility of this approach since it allows one to target locations with the highest risk (e.g., where there are lead service lines). Another acknowledged the appropriateness of using NHANES data as a resource to represent integrated estimates of environmental exposures.

The chair asked reviewers for any final comments on Charge Question 3. The following thoughts and concerns were mentioned:

- A reviewer expressed concern with the soil/dust ingestion rates and specifically noted that the ingestion rates for the 0- to 6-month age group seemed high.

  EPA Clarification: EPA confirmed that they had limited information for the 0- to 6-month age group and therefore conservatively assumed the same soil/dust ingestion rate as for 1-year-olds. EPA acknowledged that they could evaluate another scenario while zeroing out this input parameter to see how sensitive the results are.

- Three reviewers acknowledged the difficulties of these modeling tasks and expressed appreciation for the work EPA has done.

6. REVIEWER DISCUSSION: CHARGE QUESTION 4 (MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES)

Charge Question 4 (Model Evaluation and Multimedia Exposure Pathway/Sensitivity Analyses): Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on the type of sensitivity analyses that would be useful to analyze aggregate lead exposures and identify key model inputs. Please comment on the sensitivity analyses conducted for Approach 3.

The chair noted that reviewers had already discussed many of the points covered by this charge question and then began the discussion by summarizing his views in response to this question. In his opinion, the best approach in all three cases is to validate models against existing data (e.g., BLL data and any other characterizing data). This could be accomplished by taking a relatively large sample of individuals with

[15] Additional details can be found in Dr. Philip Goodrum's post-meeting comments, provided in Appendix H.

measured BLLs and collecting data on exposure factors thought to influence those levels (e.g., drinking water concentration, activity profiles, housing characteristics). External characteristics of individuals could then be matched to one another, excluding the single characteristic under investigation, and then categorized by drinking water concentration. This would allow examination of the effect of drinking water concentrations on BLLs. Alternatively, EPA could use existing data to implement a statistical rather than heuristic approach with standard regression equations, as described in the chair's post-meeting comments.[16]

In response, a reviewer recommended that EPA conduct sensitivity analyses for all parts of the proposed models, including the physiological, pharmacokinetic, and exposure parameters. Several reviewers then provided specific recommendations for sensitivity analyses:

- A reviewer recognized EPA's approach of evaluating different scenarios as a form of sensitivity analysis, and encouraged the Agency to explore the other scenarios suggested by the panel. Stratifying models by geographic area (e.g., by urban versus rural settings) was identified as one example for how to conduct these types of analyses. Another reviewer noted that the IEUBK model cannot be used effectively to describe the United States population, further emphasizing the utility of evaluating stratified portions of the NHANES database through sensitivity analysis.

- A reviewer recommended that EPA use sensitivity analysis to explore a broader definition of "childbearing age" that aligns with biological capabilities and the fact that mothers are now typically older. The reviewer also suggested sensitivity analysis for race and ethnicity

- Two reviewers suggested that EPA explore model sensitivity of the maternal BLLs. One noted that the most significant contribution of lead to formula-fed infants is from maternal blood and encouraged EPA to provide justification for using a lower maternal BLL than the default IEUBK value. The geometric mean maternal BLL (0.61 µg/dL) applied in the proposed modeling approaches is susceptible to the imputation method used for non-detects. EPA should clarify the description of related maternal BLL analyses in Section 5.10 of the Agency's report.

- A reviewer suggested that EPA use sensitivity analysis to evaluate the dust ingestion rate and amount of formula consumed by a child.

- A reviewer expressed concern that many of the IEUBK model input parameters are different than those historically used by the Agency. These markedly different inputs should be further explained by EPA and explored with sensitivity analysis.

- A reviewer noted the difficulties arising from rounding when evaluating very low levels of parameter values, which can be informed by sensitivity analysis.

Several reviewers commented on the use of probabilistic versus one-at-a-time sensitivity analysis. One expressed a preference for probabilistic methods as a way to capture simultaneous contributions of inputs. This reviewer also noted that interpretations of model sensitivity to input choices for the water pathway depend, in part, on the risk metric. Another reviewer strongly recommended that EPA conduct one-at-a-time global sensitivity analyses for the deterministic models. The one-at-a-time schemes provide information that is easier to interpret and allows for identification of variables that have the greatest impact on modeled

[16] Additional details can be found in Dr. Ryan R. Barry's post-meeting comments, provided in Appendix H.

output. For the SHEDS model, the reviewer noted that Monte Carlo simulations (with "interim" outputs appropriately saved) can provide sufficient response information for developing global sensitivity metrics. A third reviewer agreed that the approach of one-at-a-time sensitivity analysis could be used to screen variables, which could subsequently be analyzed further with probabilistic methods.

Several reviewers discussed the sensitivity analyses conducted for Approach 3. One reviewer first described the sequential steps taken by EPA in Approach 3 to evaluate the contribution of the water pathway to BLLs; EPA evaluated the BLL distribution with the water pathway included, removed the water pathway from the models, and then explored the relative contribution of water by adding different water pathway scenarios back into the model. The reviewer encouraged EPA to explore the decisions involved with the calibration step of this process (i.e., where model performance was evaluated against NHANES with water initially included) as part of the Agency's sensitivity analyses. This is particularly important since it sets the stage for the default base model. The reviewer requested EPA clarification on whether the Agency evaluated different options for this calibration exercise.

> **EPA Clarification**: EPA acknowledged that the reviewer accurately described the Agency's evaluation process. EPA first incorporated all external suggestions on inputs and algorithms and then compared model-predicted BLLs to NHANES BLLs. These results provided confidence that the Agency had successfully ground-truthed the model against the NHANES database with water data. After this evaluation, EPA plotted water lead concentrations against modeled BLLs (as shown in Slide 14 from the introductory presentation [Appendix E]) to identify where specified threshold BLLs intersected water levels. EPA noted that this is not necessarily a calibration step, but instead their process to identify "tipping points" (i.e., the concentrations of lead in water that keep BLLs below a specific value).

In response, a reviewer commented that EPA's conclusion that predicted BLLs are close enough to national NHANES BLLs using baseline inputs assumes that the geometric mean and arithmetic mean inputs, as well as the choices of probability distributions, are set. EPA performed sensitivity analyses after the baseline set of inputs was established, and then evaluated how predicted BLLs changed with different scenarios. The reviewer suggested that EPA use sensitivity analysis to identify different sets of inputs that would establish a baseline that is considered consistent with NHANES and has approximately the same error as the current approach.

Another reviewer recognized that EPA ran models using the selected inputs, determined that they could acceptably describe the NHANES database, removed water from the model, and then added water back into the model to assess relative contributions. The reviewer requested EPA clarification on how water was added back into the model.

> **EPA Clarification**: After the evaluation step, EPA modeled exposure factors and concentrations for air, dust, soil, and food, and then explored different inputs related to water to determine the concentration that resulted in the specified BLL.

The reviewer responded with concern that EPA conducted sensitivity analyses after the Agency had accepted the contribution of water, rather than as part of the evaluation. This concern was echoed by another reviewer, who suggested that EPA clarify when sensitivity analyses were completed in the modeling process. A different reviewer suggested that EPA explore multiple base models to determine whether a different choice of inputs could produce different results when the water pathway is included. For example, the reviewer questioned the impact of using input values published by von Lindern et al. (2016) as compared to those estimated by Özkaynak et al. (2011) on the BLL distribution.

A reviewer wondered if EPA's sensitivity analysis explored the impact of redefining the drinking water compartment before the rest of the analyses were run. The reviewer also noted that the models assume all

the water anyone will be exposed to across the entire United States can be adequately represented by a single concentration. Another reviewer expressed a similar concern and questioned why variability within the drinking water pathway was not considered in the modeling approaches.

> **EPA Clarification**: The Agency used the Six-Year Review drinking water compliance data as part of their evaluation and completed sensitivity analyses on baseline to understand the most sensitive inputs (e.g., by altering soil/dust ingestion rates and non-detect values for dietary lead). When determining the water lead concentration, EPA did not conduct sensitivity analyses with the Six-Year Review drinking water data. After the Agency completed their baseline runs, evaluation, and sensitivity analyses, EPA identified the maximum daily average household tap water lead concentrations that would keep BLLs below the specified values of 3.5 µg/dL and 5 µg/dL.

A reviewer responded by noting that the expected input to the IEUBK model is a long-term average. There are different simulation techniques that can be used with a stochastic front-end model to establish the long-term average intake for water. The reviewer noted three variables with probability distributions (i.e., the concentration term, consumption rate, and absorption factor) that could be explored to do so, assuming usual variability and with occasional concentration spikes.

> **EPA Clarification**: The Approach 3 (SHEDS-IEUBK) evaluation did consider variability for both drinking water intake (NHANES diaries) and water lead concentration data (Six-Year Review drinking water compliance data). To determine the water lead concentration that keeps children's BLLs below specified values for a given scenario, a point estimate daily average concentration value was determined.

A reviewer responded by noting that the use of a fixed concentration value and a mean intake value is a reasonable approach, and is the approach taken by the European community. The reviewer would support integrating variability for the water concentration term to the model as data become available. The reviewer questioned how much sensitivity analysis EPA completed for the input parameters that are directly related to water.

> **EPA Clarification**: EPA clarified that sensitivity analyses for soil and dust ingestion rates are presented in tables S8 and S9 of their draft manuscript. Since compiling that manuscript, EPA has conducted additional sensitivity analyses that the Agency offered to consolidate and provide to ERG shortly after the meeting to distribute to reviewers[17] as they prepared their individual post-meeting comments. These results indicate that inputs for the soil/dust pathway were the most sensitive parameters for 1- to 2-year-olds while inputs for water intake, water absorption rate, and water lead concentration were the most sensitive parameters for 0- to 6-month-olds.

Following these EPA clarifications, the panel chair asked reviewers to specifically comment on the strengths and weaknesses of Approaches 1 and 2. One reviewer restated the usefulness of a global sensitivity analysis for the IEUBK model to explore how changing from arithmetic means to geometric means[18] impacts output estimates. Another reviewer noted the utility of both global and local sensitivity analyses and suggested that EPA focus these analyses more heavily on Approach 3, as a lot of sensitivity analysis has already been completed for the IEUBK model.

A reviewer questioned whether there was an opportunity for EPA to explore data related to Lead Contamination and Control Act (LCCA) initiatives for measuring water quality within buildings, schools, and

[17] Upon receipt from EPA after the meeting, ERG distributed these additional sensitivity analyses (provided in Appendix I) to reviewers.

[18] As clarified earlier by EPA, Approach 3 used full distributions for model inputs and not arithmetic or geometric means.

early education facilities. The reviewer expressed an interest in seeing how the distribution of these data compares to the distribution of compliance data from the public water supply system.

> **EPA Clarification**: EPA mentioned two programs that address lead exposure; the Lead and Copper Rule, which applies to public water systems, and the LCCA, which requires EPA to develop and distribute voluntary lead sampling procedures to schools. Under the LCCA, schools are not required to report sampling results to EPA, and these school-level data are therefore not readily available to EPA.

A reviewer suggested that EPA include additional discussion in the introduction of their report on the relative importance of lead service lines as a source of lead exposure, as compared to schools. While there is limited meta-analysis of lead concentration data collected in schools in the U.S., evidence suggests that exposures in homes with lead service lines may be an order of magnitude higher than those experienced at schools. The reviewer acknowledged the value of studying school exposures, but encouraged EPA to remain focused on high-risk houses with lead service lines. In many cases, this is where exposure to lead from drinking water is significant when compared with exposures from paint, dust, and soil. The reviewer encouraged EPA to gather data from high-risk homes with lead service lines to protect the most vulnerable populations.

Several reviewers commented on weaknesses with the IEUBK model, and offered suggestions for sensitivity analysis to explore these weaknesses:

- A reviewer noted the limitation of IEUBK models when addressing short-term exposures. Equilibrium biokinetic models cannot properly process acute concentration spikes.

- Another reviewer identified the GSD lumping term as a weakness of IEUBK models and encouraged EPA to conduct sensitivity analyses for the range of GSDs represented by different scenarios and supported by empirical data. The reviewer referenced two studies published by EPA (Hogan et al. [1998] and White et al. [2008])[19] that explored the impact of GSDs and found that GSDs increased as BLLs decreased. Model sensitivity to the selected GSD is critical at the lower end of the BLL distribution.
    - A reviewer responded by questioning whether findings from Hogan et al. (1998) and White et al. (1998) are sufficient to cover the range of BLLs that EPA is considering in the proposed modeling approaches.
    - As noted by another reviewer, the impact of the GSD becomes increasingly difficult to understand as BLLs decrease. The GSD of 1.6 was developed as a consensus number so that the tool could be completed and used for regulatory analysis many years ago. The reviewer expressed concern with using a geometric mean along with a GSD of 1.6.

- Three reviewers mentioned that changes in detection limits can have a major effect on many different parameters of the distribution, including BLLs. If a distribution is truncated, all other parameters being used to describe that distribution must change.

- A reviewer asked the panel if the scenario with percentiles was therefore weaker than the scenario evaluating a fixed 0.5 µg/dL or 1 µg/dL increase in BLL. One reviewer responded by noting that

[19] Hogan, K., A. Marcus, R. Smith, and P. White. 1998. Integrated Exposure Uptake Biokinetic Model for Lead in Children: Empirical comparisons with epidemiologic data. Environ. Health Persp. 106 (Suppl 6):1557-1567.

White, P., P. Van Leeuwen, B.D. Davis, M. Maddaloni, K.A. Hogan, A.H. Marcus, and R.W. Elias. 1998. The conceptual structure of the Integrated Exposure Uptake Biokinetic Model for Lead in Children. Environ. Health Persp. 106 (Suppl 6):1513-1530.

percentiles become increasingly uncertain at higher vales when the GSD remains fixed. The reviewer stated that measures of central tendency produce better estimates for a distribution than outliers. Another reviewer mentioned that estimates of BLLs in upper percentiles are susceptible to uncertainty with the selected GSD and measure of central tendency (i.e., arithmetic mean or geometric mean).

A reviewer acknowledged the utility of emphasizing the reduction in BLLs, rather than percentiles, that can be achieved with a given change in lead concentrations in water. The children in the higher percentiles suffer multiple atypical source and exposure co-factors, that cannot be remedied by further reductions in that media concentration. On a related note, another reviewer mentioned that if interventions for lead treatment or corrosion control do not result in significant difference in percentage of children with BLLs above a certain percentile, questions arise as to whether those interventions were justified. The reviewer therefore stressed the importance of EPA ensuring the water concentration estimates for the higher percentile BLLs are solid and that all uncertainties are quantified. Related comments and concerns include:

- A reviewer commented that these concerns should be addressed in EPA's final document and stressed the need for EPA to understand the exposures that contribute to the 95th and 97.5th percentiles of the national BLL distribution. The modeling approaches should not be interpreted to mean that drinking water is the cause of all childhood lead poisonings at the upper end of the distribution. Another reviewer agreed and noted that it is unusual for a high BLL to be attributable to water.

- According to one reviewer, the most recent epidemiologic study to quantify the contribution of lead from dust, air, water, and diet was completed in Montreal where BLLs are relatively low (geometric mean = 1.45 µg/dL). This study demonstrated that children living in households with the highest percentile of lead water concentrations were at the greatest risk of elevated BLLs.[20]

For these reasons, one reviewer expressed a preference for the concept of a delta risk metric. This metric addresses the question of the relative source contribution of water and quantifies the relationship between lead concentrations in water and predicted level in BLL. The risk metric can also change in a meaningful way for children who already have a high BLL. Another reviewer similarly noted the utility of being able to predict changes in BLLs given changes in water lead concentrations.

7. REVIEWER DISCUSSION: CHARGE QUESTION 5

Charge Question 5: How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches,

[20] After the meeting, this reviewer provided this and three other references to ERG to distribute to other reviewers as they prepared their post-meeting comments:

Deshommes, E., M. Prévost, P. Levallois, F. Lemieux, and S. Nour. 2013. Application of lead monitoring results to predict 0- to 7-year-old children's exposure at the tap. Water Res; 47(7):2409-20.

Levallois, P., J. St-Laurent, D. Gauvin, M. Courteau, M. Prévost, C. Campagna, F. Lemieux, S. Nour, M. D'Amour, and P.E. Rasmussen. 2014. The impact of drinking water, indoor dust and paint on blood lead levels of children aged 1-5 years in Montréal (Québec, Canada). J Expo Sci Environ Epidemiol; 24(2):185-91.

Deshommes, E., R.C. Andrews, G. Gagnon, T. McCluskey, B. McIlwain, E. Doré, S. Nour, and M. Prévost. 2016. Evaluation of exposure to lead from drinking water in large buildings. Water Res; 99:46-55.

Deshommes, E., L. Laroche, D. Deveau, S. Nour, and M. Prévost. 2017. Short- and long-term lead release after partial lead service line replacements in a metropolitan water distribution system. Environ Sci Technol; 51(17): 9507-9515.

how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

The panel chair noted that reviewers had identified several partitioning scenarios that would be beneficial to understanding the association between drinking water concentrations and BLLs (e.g., geographic area, age of housing, presence of lead service lines). Reviewers were asked to further discuss these scenarios and provide additional suggestions:

- A reviewer mentioned the previous suggestion of developing scenarios that examine different portions of the NHANES BLL distribution. The reviewer encouraged EPA to use these types of scenarios to explore the relative contribution of lead in drinking water to elevated BLLs in a systematic way. This could be done by modeling scenarios for geographic areas where elevated BLLs are central to the probability distribution, as well as areas where elevated BLLs fall at the high end of the distribution. The relative importance of the drinking water pathway depends on the community scenario being evaluated.

- A reviewer suggested that EPA evaluate different iterations of exposure duration to represent a child's exposure at school (i.e., 8-hour exposures). While recognizing issues related to data generalizability and varying sampling protocols, the reviewer encouraged EPA to contact jurisdictions that have collected and evaluated school data in a systematic way to support this evaluation. Women of child-bearing age (e.g., students or faculty) could also be considered in a school-based scenario. Another reviewer commented on the challenges of separating water consumption between time spent at home and at school. Future work is needed to quantify the importance of lead in drinking water at schools and childcare facilities.

- Certain events can trigger a change in the pH or hardness of water, as noted by one reviewer. It would be useful to understand how these events affect the distribution of lead in drinking water, uptake of lead by the body, and resulting BLLs in a community. Another reviewer agreed and stressed that these events can last for weeks, and sometimes months.

- A reviewer suggested that EPA model the full range of potential contributions of the water pathway relative to other pathways, for several scenarios. These simulations would provide a distribution of what the contribution of water might be, given environmental conditions within a certain community.

Several reviewers were concerned with how EPA will use the modeled number or benchmark:

- A reviewer questioned how EPA will respond when lead concentrations are detected above the modeled benchmark, noting the importance of this question when evaluating the different model input parameters. It is critical that EPA develop exposure indices that are appropriate for the intended use of the modeled output. The reviewer also questioned how EPA will identify and assess poor communities, where additional exposures to lead are particularly concerning.

- A reviewer noted that these discussions assume that elevated BLLs, at all levels, result in a biological effect. Related to this point, the reviewer questioned how well the 3.5 µg/dL and 5 µg/dL levels (i.e., reference level based on the 97.5th percentile of BLLs among children) could be used to evaluate the 0- to 6-month age group. It is important for EPA to clearly define the health-based benchmark in terms of the health effect it represents

- A reviewer noted that EPA will need to develop a protocol to relate a single measured concentration of lead in water to the longer-term 30-day average concentration represented by the modeled output. The reviewer expressed concern that the current modeling approach might produce a number that requires response agencies to conduct unnecessary follow-up sampling.

- The proposed modeling approaches, as stated by one reviewer, present an opportunity to estimate different IEUBK deterministic BLL outputs based on various exposure inputs covering the expected distribution for a community or school. The reviewer suggested that EPA consider developing a heat map for these outputs, which could be used to prioritize affected schools or communities within a distribution system[21]. One axis of the map could represent probable water intake values, while the other could characterize probable concentrations of lead in drinking water. These heat maps would complement risk communication and provide useful information to share with local communities. The reviewer encouraged EPA to develop heat maps for several different scenarios (e.g., children ages 5 to 7 years, infants ages 0 to 6 months, women of child-bearing age). Another reviewer recommended that EPA develop a heat map for various non-drinking water exposure factors as a tool to help parents identify ways to reduce lead exposure for their children.

- A reviewer encouraged EPA to consider an anticipatory rulemaking approach for lead in drinking water similar to that sometimes used in the occupational arena. For example, protective measures are required, as part of California's Lead in Construction standard, for construction workers assigned to certain tasks that are expected to raise BLLs. As part of this rule, the burden is put on employers to demonstrate that they have sufficiently protected their workers before the need to monitor them can be removed.

- There are many metrics that can be evaluated to understand the baseline characteristics of a community and the environmental contributions of lead, as noted by one reviewer. He suggested that EPA explore the utility of childhood lead poisoning data for this purpose.

The panel chair asked reviewers to comment on suggested short-term and long-term steps for EPA to consider in further development of the three proposed modeling approaches:

- A reviewer suggested that EPA evaluate how BLLs change among women with multiple pregnancies. In addition, this reviewer encouraged EPA to conduct Monte Carlo simulations to understand how variability in water concentrations and baseline conditions may impact predicted BLLs.

- In the near-term, a systematic quantitative uncertainty analysis would greatly strengthen EPA's report, according to one reviewer. If sufficient data are not available for two-dimensional Monte-Carlo sensitivity analyses, a targeted sensitivity analysis that estimates maximum bounds would be an improvement over the qualitative statements currently provided in the report. In the long term, the reviewer suggested that EPA develop a more comprehensive PBPK model that incorporates physiological and biochemical changes across multiple life stages.

[21] Additional details and several hypothetical heat maps can be found in Dr. Marc Nascarella's post-meeting comments, provided in Appendix H.

- A reviewer recommended that EPA expand their sensitivity analyses in an iterative manner to bound the upper and lower predicted BLL estimates. As part of this process, EPA could model upper bound estimates for a scenario representing a child that spends part of his/her time at home and at a daycare facility/school, with different consumptions rates and water concentrations at each location. The reviewer also suggested that EPA model an acute exposure scenario and consider prior modeling exercises conducted by the Agency that have explored the relative impact of spikes on longer-term average lead exposures.

- A reviewer expressed interest in further understanding how the proposed modeling approaches respond to the removal of exposure sources; in her experience, pharmacokinetic models respond differently to increases and decreases in exposure. The reviewer also encouraged EPA to look at anticipatory events and agreed with the suggestion to develop heat maps. In addition, there are other possible drivers of elevated BLLs than soil, dust, water, and diet that EPA should consider in their proposed modeling approaches (e.g., take-home exposures, candy, ceramics).

- A reviewer recommended that EPA develop more sophisticated soil and dust lead concentration input variables for all three modeling approaches. The reviewer noted that there is less variability in aggregated soil and dust concentrations than each of the individual elements, and that house dust reflects community exposures and the age of a house more so than soil. The reviewer recommended that EPA develop an aggregate soil and dust concentration, as a function of house age. Another reviewer commented that remediation of soil can change the distribution and correlation structure between lead in soil outside a house and lead in dust inside a house. To follow up on this point, a reviewer requested EPA clarification on whether soil/dust lead concentrations were modeled as separate distributions, as well as the basis for those distributions.

  EPA Clarification: As shown on Slide 9 (Appendix F) from the introductory presentation and in table S3 of EPA's paper, the Agency fit empirical distributions for soil and dust to data from HUD's American Healthy Homes survey. These data were stratified and weighted in the SHEDs model by the age of housing (e.g., pre- and post-1950). The models included a correlation coefficient of 0.48 for dust and soil concentrations.

- A reviewer encouraged EPA to evaluate lead service line data to support interpretation at the high end of the BLL distribution and to model extreme events that sometimes occur in a water distribution system. The reviewer also recommended that EPA include additional discussion on selected water ingestion rates and justification for why they differ from historical default values. In addition, the reviewer suggested that EPA explore drinking water data from HUD for high-risk homes and review related studies from AWWA on this topic. The reviewer encouraged EPA to integrate information on the variability of water concentrations, acute releases, and prevalence or probability of lead service lines, to the extent possible.

EPA requested clarification from the panel on several points.

EPA Clarification: For this review, the panel has been asked to scientifically review a work product that will ultimately inform a regulatory policy. Many of the recommendations provided by the panel will be useful as the Agency moves forward with developing that policy, while others are beneficial to the long-term advancement of the model. EPA requested that reviewers distinguish, in their post-meeting comments, the degree to which their recommendations are better suited for one purpose over the other. EPA also requested additional discussion on the variability of lead concentrations across water

systems and through time, as episodic events take place. The Agency noted that water systems are required to have optimized corrosion control treatment and to regularly monitor water quality parameters in their distribution system on a regular basis; these activities are the primary means by which temporal increases in lead levels are prevented. EPA recognizes that there are other sources of lead exposure in houses, but that the Agency's goal is to identify a concentration of lead in drinking water that should prompt action.

A reviewer responded by acknowledging the challenges of comparing results from a discrete grab sample to modeled output that represents a longer-term average. The reviewer requested EPA clarification on whether the panel should suggest approaches that account for spike concentration or exposures that occur outside the home.

EPA Clarification: This question presupposes that EPA could devise a monitoring scheme that would capture those spikes within the Agency's policy, which would be challenging. A sampling structure that captures these data does not currently exist.

In response, a reviewer requested clarification regarding what EPA does after a concentration spike is detected in a distribution system.

EPA Clarification: This is a policy question that the Agency is exploring. When high concentrations of lead are measured in a water distribution system, follow-up sampling is a logical first step. The actions that follow that sampling are based on the availability of tools to reduce exposure (e.g., corrosion control refinements). If the spike is event-related, mitigations include flushing, point of use filters to remove lead, and lead service line replacement.

8. REVIEWER DISCUSSION: REVIEWER CLOSING REMARKS

At the end of the meeting, the panel chair asked each reviewer to provide individual closing remarks.

- A reviewer acknowledged the utility of the proposed modeling approaches to identify and mitigate problems related to lead in drinking water. This reviewer recommended that EPA further discuss uncertainty in spatial and temporal variation, data limitations, definitions for key terms, and all underlying modeling assumptions in their final report.

- The next reviewer acknowledged EPA's hard work in developing three credible approaches that begin to characterize some of the uncertainty when regulating lead. The reviewer encouraged EPA to continue to develop these modeling approaches with the homeowner in mind and highlighted the importance of considering exposure duration in future model iterations.

- Another reviewer commended EPA scientists for their hard work and commented that all three approaches offer different but useful information. The reviewer expressed a preference for Approach 3 and noted that it could be improved by linking in a PBPK model. The reviewer encouraged EPA to use consistent input parameters and carefully consider how modeled output will be communicated to the public. The modeled approaches that are currently applicable to the general population could be expanded by targeting populations in geographic locations that are at the greatest risk

- The fourth reviewer thanked the EPA team for their work and clarification throughout the meeting. The reviewer suggested that EPA explore other scenarios by targeting communities at both the high

and low end of the BLL distribution. The reviewer expressed appreciation for the diversity of the panel and mentioned that they will provide additional information on probabilistic sampling event techniques, as well as soil/dust ingestion rates and concentrations in their post-meeting comments.

- The next reviewer thanked the EPA team for their thoroughness and decorum throughout the meeting. He expressed concern with the use of exposure factors that are not consistent with the input parameters historically used by the Agency and encouraged EPA to carefully consider how to communicate the modeled numbers to the public without causing unnecessary concern.

- The sixth reviewer appreciated the intellectual challenges of the proposed modeling approaches and recognized EPA's top-tier modeling team. The reviewer expressed concern with the use of input parameters that are inconsistent with historical applications of the models and how the modeled output will be presented to and interpreted by the public. The reviewer expressed a preference for the SHEDs modeling approach.

- The next reviewer commended the EPA team for their hard work on the proposed modeling approaches. The reviewer suggested that, in the short term, EPA prioritize strengthening the analyses for the 0- to 6-month age group. The reviewer recommended that EPA add information to the beginning of their report on the water distribution data that were used and the lead-profiling data that are available. The reviewer also encouraged EPA to incorporate complementary analysis on acute exposure scenarios and to explicitly mention that the data used for the SHEDs modeling approach do not account for extreme events (e.g., Flint, Michigan). The reviewer expressed concern with the disconnect between a BLL threshold and an acceptable mean level of lead in drinking water. This disconnect may result in endorsement of high acceptable levels of lead in drinking water at homes with lead service lines.

- The final reviewer praised the EPA team and affirmed the utility of the three proposed modeling approaches for understanding the effects from lead in drinking water. He recommended that EPA consider adding pre-natal exposures and some type of stratification (e.g., geographic, temporal) to the models.

The chair thanked EPA for accommodating the panel's questions, the panel for their collegiality, and ERG for gathering a diverse panel. Connery reminded reviewers that their final task for the review was to provide their final individual written post-meeting comments to ERG for inclusion in the meeting summary report (Appendix H). She thanked the panelists for serving as reviewers and closed the meeting.

Appendix A

LIST OF PEER REVIEWERS AND BIOGRAPHICAL SKETCHES

United States
Environmental Protection Agency

Peer Review Meeting for EPA's Draft Report: Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

St. Gregory Hotel
Washington, DC
June 27-28, 2017

Reviewers

Panos Georgopoulos, Ph.D.
Professor, Department of Environmental and Occupational Health
Rutgers University
Piscataway, NJ

Philip Goodrum, Ph.D., DABT
Senior Managing Scientist
Integral Consulting, Inc.
Fayetteville, NY

Ian von Lindern, Ph.D.
Executive Director
TerraGraphics International Foundation
Moscow, ID

Anne Loccisano, Ph.D.
Senior Scientist
Exponent, Inc.
Alexandria, VA

Marc A. Nascarella, Ph.D.
Director, Environmental Toxicology Program
Bureau of Environmental Health
Massachusetts Department of Public Health
Boston, MA

Michèle Prévost, Ph.D.
Senior Chair holder
NSERC Industrial Chair on Drinking Water
Polytechnique Montreal
Montreal, Quebec, Canada

P. Barry Ryan, Ph.D. (Chair)
Professor, Department of Environmental Health
Rollins School of Public Health
Emory University
Atlanta, GA

Kathleen L. Vork, MPH, Ph.D.
Staff Toxicologist
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Oakland, CA

1. P. Barry Ryan, Ph.D., Emory University, Rollins School of Public Health

i. *Relevant Expertise Areas:* Exposure science; environmental lead exposure analyses; SHEDS multimedia modeling; modeling exposure pathways.

ii. *Education:* Wesleyan University, Ph.D. in Computational Chemistry (1979) and University of Chicago, M.S. in Physical Chemistry (1975).

iii. *Professional Experience:* Dr. P. Barry Ryan is Professor of Exposure Science and Environmental Chemistry in the Rollins School of Public Health at Emory University, with a joint appointment in the Department of Chemistry. He has been active in the exposure assessment field for more than 30 years, publishing over 125 peer-reviewed manuscripts and book chapters and presenting to the scientific community on more than 200 occasions. He has conducted numerous cross-sectional and longitudinal studies of community-based exposures, for multiple pollutants and in multiple media, and associated human health effects. Dr. Ryan is currently Dual Principal Investigator for the National Institute of Environmental Health Sciences (NIEHS)/USEPA co-funded Children's Environmental Health Centers' Center for Children's Health, the Environment, the Microbiome and Metabolomics (C-CHEM2). His team is researching the influence of environmental exposures on the microbiome and neurodevelopment of infants and children. Dr. Ryan is also an active participant in the NIH-funded Children's Health Exposure Analysis Resource (CHEAR) program, and the NIH/Gates Foundation International Household Air Pollutant Intervention (HAPIN) Trial. In addition, he was previously Co-Principal Investigator and Co-Investigator on three separate Formative Research projects associated with the National Children's Study. He was also Principal Investigator on a USEPA-funded longitudinal study of exposures to pollutants known as the National Human Exposure Assessment (NHEXAS) - Maryland study, and a USEPA-funded study to evaluate lifetime bone-lead burden among adolescents in two different cities. Dr. Ryan was member of the Board of Scientific Counselors for EPA's Office of Research and Development and a member of the EPA Science Advisory Board Sub-Committee on Exposure and Human Health. He also completed a four-year term on the Federal Advisory Committee for the National Children's Study undertaken by the National Institutes of Health. Over the course of his career, he has served on numerous other advisory panels for EPA, most recently on the external evaluation committee reviewing the EPA Guidelines for Human Exposure.

2. Panos Georgopoulos, Ph.D., Rutgers University

i. *Relevant Expertise Areas:* PBPK modeling; exposure assessment; probabilistic exposure modeling; modeling exposure pathways.

ii. *Education:* California Institute of Technology, Ph.D. in Chemical Engineering (1986) and M.S. in Chemical Engineering (1982).

iii. *Professional Experience:* Dr. Georgopoulos is Professor of Environmental and Occupational Health at Rutgers University specializing in mathematical modeling of environmental and biological systems. He directs the Informatics and Computational Core for the NIEHS Center for Environmental Exposures and Disease within Rutgers' Environmental and Occupational Health Sciences Institute (EOHSI). Dr. Georgopoulos established and directs the Computational Chemodynamics Laboratory at EOHSI, a state-of-the-art facility for informatics and modeling of complex environmental and biological systems. He also directs the Center for Exposure and Risk Modeling and is Co-Director of the Environmental Bioinformatics and Computational Toxicology Center, a research consortium of Rutgers University, Princeton University, and the Food and Drug Administration's (FDA's) Center for Toxicoinformatics. Dr. Georgopoulos previously served as Director of the Department of Energy (DOE)-funded Center of Expertise in Exposure Assessment of the Consortium for Risk Evaluation with Stakeholder Participation. His research interests include environmental health informatics,

systems modeling, human exposure, and risk analysis. He has researched on topics including mathematical modeling of multimedia fate and transport of environmental pollutants, multi-pathway modeling of human exposure to chemicals agents, and individual and population-based simulation modeling of contaminant uptake in residential and occupational settings. Dr. Georgopoulos has published more than 125 peer-reviewed articles and chapters in scientific journals, books and proceedings on these topics and others, and has authored or co-authored several state and federal government documents and technical reports. He served on the external peer review committee for EPA's Technical Approach for Lead (2014) and currently serves as a member of various scientific and technical committees on other environmental issues, including EPA's Chemical Safety Advisory Committee. Dr. Georgopoulos has published and presented PBPK modeling and probabilistic multi-pathway exposure and uptake modeling of multimedia contaminants, including lead and co-occurring metals.

3. Philip Goodrum, Ph.D., Integral Consulting, Inc.

i. *Relevant Expertise Areas:* Environmental lead exposure analyses; probabilistic modeling; IEUBK modeling; modeling exposure pathways.

ii. *Education:* SUNY College of Environmental Science and Forestry, Ph.D. in Environmental Engineering (1999) and M.S. in Water Resources Engineering (1995).

iii. *Professional Experience:* Dr. Philip Goodrum is a senior managing scientist at Integral Consulting, Inc., with more than 25 years of experience in quantitative risk assessment and environmental modeling. He specializes in applications to human health and ecological risk assessment, sediment remediation, groundwater compliance monitoring, and natural resource damage assessment. Dr. Goodrum is a recognized national leader in statistical sampling methods, probabilistic risk assessment, and lead exposure modeling. He has developed strategies to characterize and manage risks associated with environmental contaminants, and represented clients in negotiations with state and federal regulators, trustees, and stakeholder groups on issues related to data interpretation, statistical analysis, modeling, and risk characterization. He has assisted EPA, state agencies, and other clients in the interpretation of results of statistical analysis applied to empirical data and environmental model simulations. For example, he co-authored EPA's 2001 Risk Assessment Guidance for Superfund (RAGS), which provides guidance on the application of probabilistic risk assessment in human health and ecological risk assessment and served as independent reviewer of a probabilistic risk assessment conducted by EPA Region 1. While working at Scientific and Regulatory Consultants (SRC), he was responsible for writing technical support documents for EPA on the use of the IEUBK model and managing EPA's "hotline" for users of the software. He also developed the Integrated Stochastic Exposure model, a software tool that applies Monte Carlo analysis to explore variability and uncertainty in estimates of blood lead concentrations in children. Dr. Goodrum has published numerous articles in peer-reviewed journals and served on several advisory committees related to lead and health, including the EPA Science Advisory Board for Lead (2010-2015), EPA Clean Air Scientific Advisory Committee Lead Review Panel (2006-2007), and EPA National Center for Exposure Assessment Peer Review Panel for All Ages Risk Model for Lead (2000).

4. Ian von Lindern, Ph.D., TerraGraphics International Foundation

i. *Relevant Expertise Areas:* Exposure assessments; probabilistic modeling; IEUBK modeling; modeling exposure pathways.

ii. *Education:* Yale University, Ph.D. in Environmental Science and Engineering (1980) and M.S. in Biometeorology and Atmospheric Studies (1973).

iii. *Professional Experience:* From 1984 through his retirement in 2014, Dr. Ian von Lindern served as Chief Executive Officer and Principal Scientist of TerraGraphics Environmental Engineering Inc., whose principal clients were state, federal, and local governments. He currently serves as co-founder and Executive Director of TerraGraphics International Foundation (TIFO), a 501(3)(c) non-profit organization that provides humanitarian assistance to communities, governments, and NGOs concerning health and environmental response to toxic chemical and hazardous waste exposures. This work has included educational and advisory roles in lead poisoning health response activities in many different countries, including characterization and remediation of environmental lead exposures in contaminated communities suffering from childhood lead poisoning in northern Nigeria. Dr. von Lindern brings over 40 years of national and international engineering and scientific expertise experience, including a variety of environmental assessments; studies in air, water, and soil pollution; toxic and hazardous materials investigations; human health risk assessments; and application of statistical analysis techniques to multidisciplinary environmental problems. Over the course of his career, he has worked on projects regulated under federal, state, local, and foreign authorities; provided litigation support and expert witness testimony in administrative and court proceedings; served on several U.S. government advisory panels, and published in peer-reviewed journals on topics related to lead health risk assessment. For example, as lead risk assessor in projects involving the Bunker Hill/Coeur d'Alene Basin Superfund Site, he acquired extensive experience applying exposure and biokinetic lead modeling to assess human health risk, including site-specific quantitative analysis of the relationship between observed blood lead levels and environmental variables. He has participated in several EPA review panels specifically focused on the IEUBK model and has used the model in professional applications for 30 years. Dr. von Lindern served as an EPA Science Advisory Board member for the Review Subcommittee for Urban Soil Lead Abatement Demonstration Project (1993), Subcommittee Assessing the Consistency of Lead Health Regulations in EPA Programs (1992), Review Subcommittee Assessing the Use of the Biokinetic Model for Lead Absorption in Children at RCRA/CERCLA Sites (1988), the Ad Hoc All-Ages Lead Model Review, and the Clean Air Science Advisory Committee reviews of the National Ambient Air Quality Standard for Lead Panel (1975-77, 1982-86, and 2006-2008).

5. Anne Loccisano, Ph.D., Exponent

i. *Relevant Expertise Areas:* PBPK modeling; IEUBK modeling for lead; risk assessment.

ii. *Education:* Duquesne University, Ph.D. in Physical Chemistry (2007).

ii. *Professional Experience:* Dr. Loccisano is a board-certified toxicologist at Exponent specializing in the development and application of computational modeling techniques, such as pharmacokinetic models, PBPK models, and probabilistic human health risk assessments. She has applied these types of models to various environmental toxicants (including pesticides, metals, and perfluorinated surfactants) and consumer products to predict human exposures and the resulting risks. Her areas of expertise include human health risk assessment, toxicokinetics, product stewardship, and computational chemistry. Prior to joining Exponent, Dr. Loccisano was a Senior Scientist and Toxicologist with Reynolds American, Inc., where she performed exposure assessments, as well as deterministic and probabilistic risk assessments of consumer products in support of regulatory submissions. She contributed to the development of reference risk values and cancer slope factors for various constituents found in consumer products in order to support risk assessments for regulatory compliance. During her postdoctoral work at EPA's National Center for Environmental Assessment/ Integrated Risk Information System (IRIS), Dr. Loccisano developed and applied PBPK models to various chemicals of agency concern. She also contributed to several chemical assessments through evaluation of dose-response, mode-of-action, and toxicokinetic data. During her postdoctoral work at the Hamner Institutes, Dr. Loccisano developed and applied PBPK models for perfluorinated surfactants (PFOA and PFOS) for several species and life stages for use in human health risk assessment. Dr. Loccisano has published

numerous peer-reviewed articles and book chapters, participated as an expert reviewer, presented at national and international meetings, and is an active member of several professional societies. She has experience using the O'Flaherty PBPK model for lead and the IUEBK model, and brings an understanding of pharmacokinetics of lead during various life stages.

6. Marc A. Nascarella, Ph.D., Massachusetts Department of Public Health

i. *Relevant Expertise Areas:* Quantitative exposure assessment; IEUBK modeling; modeling exposure pathways.

ii. *Education:* University of Massachusetts Amherst, Ph.D. in Public Health Toxicology/Epidemiology (2008) and M.S. in Environmental Health/Public Health Toxicology (2002).

iii. *Professional Experience:* Dr. Marc Nascarella currently serves as Director of the Environmental Toxicology Program at the Massachusetts Department of Public Health where he directs a team of human health scientists that are responsible for quantitative assessments of exposures to contaminants in environmental media (e.g., air, water, soil, food), biomonitoring specimens (e.g., blood, urine), and consumer products. He also serves as Principal Investigator for the Biomonitoring Massachusetts Study, a statewide surveillance effort focused on identifying individuals with elevated concentrations of metals (e.g., lead, mercury, manganese, cadmium) in blood and urine, and as the Massachusetts's Department of Public Health designee on technical matters related to the regulation of drinking water quality. His work in the areas of regulatory toxicology and dose-response modeling has been presented at scientific meetings and published in government reports, peer-reviewed journals, and books. For example, he recently presented PBPK modeling results of pediatric lead poisoning that was performed as part of a clinical collaboration to evaluate a case of severe lead poisoning at the 2016 North American Congress of Clinical Toxicology (NAACT) Annual Meeting. He has extensive experience as a collaborative member on a number of biomonitoring and risk assessment committees, including the CDC/American Public Health Laboratory Association National Biomonitoring Network Steering Committee, and has been invited by CDC to speak at national meetings on toxicology and biomonitoring. His work on quantitative probabilistic modeling and dose-response assessment has been recognized by national and international professional organizations, including the International Dose-Response Society, Society of Toxicology's Risk Assessment Specialty Section, and Society for Risk Analysis' Dose-Response Specialty Group.

7. Michèle Prévost, Ph.D., Polytechnique Montreal

i. *Relevant Expertise Areas:* Environmental lead exposure analyses; modeling exposure pathways.

ii. *Education:* Polytechnique Montreal, Ph.D. in Civil Engineering (1991) and Ecole Polytechnique de Montreal, M.S. in Environmental Engineering and Civil Engineering (1984).

iii. Professional Experience: Dr. Prévost has more than 25 years of experience in the areas of water treatment and distribution. Since 1992, she serves as Industrial Chair on Drinking Water of the National Science and Engineering Council of Canada (NSERC) at the Department of Civil Engineering of Polytechnique Montreal. Dr. Prévost has completed applied research and development on source protection, water and various aspect of distribution systems (lead control, biostability, pathogen regrowth, integrity and intrusion, data mining, hydraulic and quality modeling). Recently, she directed the multi-university utility partnership initiative to reduce lead at the tap through a suite of laboratory, field, and epidemiological studies in Canada. She has directed studies and graduate students in studies on: field monitoring sampling comparing various investigative and compliance protocols, exposure assessment, epidemiological studies using blood lead measurements, application of IEUBK, and particulate lead occurrence and bioavailability. Dr. Prévost is

active on numerous technical advisory committees to utilities and international organizations and is a reviewer for several international journals. She was a member of the technical advisory committee to the Walkerton Commission and presided the Quebec RESEAU Advisory Committee on Drinking Water Regulations for 12 years. She currently serves as a member of the Pew Charitable Trusts advisory committee for development of a report evaluating the health and equity impacts of policies to prevent and respond to childhood lead exposure. An internationally recognized expert, she has authored or co-authored more than 150 publications in peer-reviewed journals that addressed lead detection, lead control, water quality in distribution systems, and health impacts, and participated in over 350 regional, national, and international conferences, many as a guest speaker. With extensive industrial experience in consulting and technology development with manufacturers, Dr. Prévost has also been active in numerous technical advisory committees to utilities and international organizations (IUVA, IWA, AWWA, etc.) and serves as a reviewer for international journals (Water Research, EST, etc.). She received several awards from AWWA, including AWWA's 2016 A.P. Black Research award for outstanding research contributions to water science and water supply rendered over an appreciable period of time.

8. Kathleen L. Vork, Ph.D., California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA)

i. *Relevant Expertise Areas:* PBPK modeling; probabilistic modeling; modeling exposure pathways.

ii. *Education:* University of California at Berkeley, Ph.D. in Environmental Health Sciences (2003) and University of Minnesota, M.P.H. in Occupational and Environmental Health (1988).

iii. *Professional Experience:* Dr. Kathleen Vork has worked at the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) for over two decades, first as a research scientist and currently as a Staff Toxicologist. Prior to OEHHA, Dr. Vork worked for the California Childhood Lead Poisoning Prevention Program. Dr. Vork has extensive experience and expertise relating to exposure pathways and the pharmacokinetics of lead in workers and the general population. Dr. Vork has implemented various statistical and mathematical modeling methods to estimate, adjust, and check the accuracy and consistency of predictions from models combining exposure pathways with PBPK and biokinetic models. She is the primary author of the report entitled "Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model" (2013). She has conducted work involving the derivation of human lactation transfer coefficients for various chemicals including lead for the "Risk Assessment Guidelines Technical Support Documents for Exposure Assessment and Stochastic Analysis" (2012) and contributed work published in "The Derivation of Non-cancer Reference Exposure Levels" (2007) for the California Air Toxics Hot Spots Program. Dr. Vork has worked collaboratively with multiple agencies, professional groups, and the public. For example, she has served on California's Advisory Committee for Training Regulations for Lead Paint Abatement for the California Lead Poisoning Prevention Program, the Lead Training Course Planning Committee for the Alameda County Lead Poisoning Prevention Program, and as a member of the Board of the Genetic and Environmental Toxicology Association of Northern California. Recently, she served on the Peer Review Panel for EPA's Approach for Estimating Exposures and Incremental Health Effects from Lead due to Renovation, Repair, and Painting Activities in Public and Commercial Buildings (2014-2015), and as a reviewer for preliminary modeling work conducted by EPA Office of Research and Development's National Exposure Research Laboratory (2016).

Appendix B

CHARGE TO PEER REVIEWERS

LEAD IN DRINKING WATER MODELING
EXTERNAL PEER REVIEW
CHARGE TO REVIEWERS

The U.S. Environmental Protection Agency's (EPA) Office of Water is considering revisions to the National Primary Drinking Water Regulations for Lead and Copper (LCR) to improve public health protection by making changes to rule requirements under the Safe Drinking Water Act. EPA has engaged stakeholder groups and the public to inform revisions to the LCR. As part of this work, the EPA's National Drinking Water Advisory Council's (NDWAC) Lead and Copper Rule Working Group was formed to provide advice to the Administrator on recommendations to strengthen public health protections of the LCR.

In December 2015, the NDWAC provided a number of specific recommendations to the EPA Administrator for LCR revisions, one recommendation is the establishment of a *household action level* "based on the amount it would take an infant to have a blood lead level (BLL) greater than five micrograms per deciliter (µg/dL) based on consumption by an average, healthy infant of infant formula made with water" (Lead and Copper Rule Working Group, 2015, p. 37). The NDWAC recommended that water systems be required to notify the consumer, the state drinking water program and the local public health agency if this level were exceeded, with the expectation that individuals and local health officials will use this information to take prompt actions at the household level to mitigate lead risks. To reduce confusion with the existing LCR system-wide "action level," EPA will use the terminology health-based benchmark to refer to this concept.

While EPA has not yet determined the specific role of a health-based benchmark for lead in drinking water in the revised LCR, the Agency sees value in providing states, drinking water systems and the public with a greater understanding of the potential health implications for vulnerable populations of specific levels of lead in drinking water. EPA anticipates that the proposed rule will consider the health-based benchmark approach recommended by the NDWAC, but this value could also help to inform other potential elements of a revised rule – including public education requirements, prioritization of households for lead service line replacement (LSLR) or other risk mitigation actions at the household level, and potential requirements related to schools.

EPA has developed three potential scientific modeling approaches to define the relationship between lead levels in drinking water and BLLs, particularly for sensitive life stages such as formula fed infants and children. These modeling approaches, as described in the draft document "Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water," are the subject of this peer review, which will inform future consideration of a health-based benchmark for the LCR revisions. Note that the modeling approaches are intended to provide scientific understanding for the LCR rulemaking, but do not anticipate or prejudge those policy decisions.

EPA is considering three approaches that model lead in drinking water's effect on BLLs using a range of exposure scenarios. All the approaches employ the Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children. Approaches 1 and 2 are individual-based approaches that look at the increase in the probability that a child would have an elevated BLL (EBLL) and a child's incremental increase in BLL, respectively. Approach 3 is a population-based probabilistic approach that evaluates the drinking water lead concentrations that would keep BLLs at particular percentiles of a simulated national distribution of different aged children. It uses the probabilistic Stochastic Human Exposure and Dose Simulation (SHEDS) Multimedia model coupled with IEUBK.

The values applied in the approaches and the results derived from the models are for illustrative purposes only. They do not indicate EPA policy decisions and are not, in and of themselves, the focus of this peer review.

EPA is seeking comments on the scientific aspects of these potential modeling approaches to associate lead in drinking water with BLLs.

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.
b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.
c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES
Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

Appendix C

LIST OF OBSERVERS

United States
Environmental Protection Agency

Peer Review Meeting for EPA's Draft Report: Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

St. Gregory Hotel
Washington, DC
June 27-28, 2017

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Appendix D

PEER REVIEW MEETING AGENDA

United States
Environmental Protection Agency

Peer Review Meeting for EPA's Draft Report: Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

St. Gregory Hotel
2033 M Street, NW
Washington, DC
June 27 - 8:30 AM to 5:30 PM
June 28 - 8:00 AM to 2:00 PM

Agenda

Tuesday, June 27

8:00 a.m. **Registration**

8:30 a.m. **Welcome, Introductions, Meeting Purpose & Agenda** ..... *Jan Connery, ERG*

8:50 a.m. **EPA Welcome Remarks**..... *Eric Burneson, Director, Standards and Risk Management Division, U.S. EPA*

9:00 a.m. **EPA Overview of Approaches 1 and 2** ..... *Ahmed Hafez, U.S. EPA*

9:20 a.m. **EPA Overview of Approach 3**..... *Valerie Zartarian, ORD, U.S. EPA*

9:40 a.m. **Public Statements** ..... *Jan Connery, ERG*

10:10 a.m. **Reviewer Discussions**..... *Barry Ryan (Chair) & Panel*

Charge Question 1: Model Scenarios ..... *Barry Ryan & Panel*

a) Strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years.

b) Are there additional life stages that should be considered by EPA?

c) Strengths and weaknesses of the modeling scenarios conducted (i.e., exposure scenarios for drinking water only and all pathways, and target BLLs [3.5 µg/dL and 5 µg/dL at several upper tail percentiles of the population]).

d) Additional scenarios that would add utility.

10:45 a.m. BREAK

11:00 a.m. **Charge Question 1: Model Scenarios (cont.)** ..... *Barry Ryan & Panel*

12:35 p.m. LUNCH

Tuesday, June 27

1:35 p.m. **Charge Question 2: Model Inputs** ..... *Barry Ryan & Panel*

a) Strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches.

b) Data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates.

c) Appropriateness of the water consumption rate based on NHANES data for this modeling effort.

d) Soil/dust ingestion rate and other key factors.

3:15 p.m. BREAK

3:30 p.m. **Charge Question 2: Model Inputs (cont.)** ..... *Barry Ryan & Panel*

3:55 p.m. **Charge Question 3: Modelling Approaches** ..... *Barry Ryan & Panel*

a) Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

b) Comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

c) i) Comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK).

ii) Comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

5:30 p.m. ADJOURN

Wednesday, June 28

8:00 a.m. **Recap of Day 1**, **Day Two Agenda and Logistics**..... *Jan Connery, ERG*

8:10 a.m. **Charge Question 3: Modelling Approaches (cont.)** ..... *Barry Ryan & Panel*

8:40 a.m. **Charge Question 4: Model Evaluation and Multimedia Exposure Pathway/Sensitivity Analyses**..... *Barry Ryan & Panel*

a) Strengths and weaknesses of the three approaches considering existing blood lead data.

b) Strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway.

c) What type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs?

d) Sensitivity analyses conducted for Approach 3.

9:30 a.m. BREAK

9:45 a.m. **Charge Question 4: Model Evaluation and Multimedia Exposure Pathway/Sensitivity Analyses**..... *Barry Ryan & Panel*

11:00 a.m.	**Charge Question 5**.....*Barry Ryan & Panel* a) How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? b) For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?
11:30 a.m.	BREAK
Noon	**Charge Question 5 (cont.)**.....*Barry Ryan & Panel*
1:15 p.m.	**Individual Reviewer Closing Comments** .....*Barry Ryan & Panel*
1:55 p.m.	**Closing Remarks** .....*Jan Connery, ERG*
2:00 p.m.	ADJOURN

Appendix E

EPA OVERVIEW OF APPROACHES 1 AND 2

Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

Peer Review | June 27-28, 2017

Expert Peer Review

- EPA is conducting expert review of the scientific aspects of three potential modeling approaches to associate lead in drinking water with BLLs, particularly for sensitive life stages such as formula fed infants and children.
- The expert peer review of these approaches will inform future consideration of a health based benchmark for the Lead and Copper Rule (LCR) revisions.
- EPA has not yet determined the specific role of a health based benchmark for lead in drinking water in the revised LCR.
- The models are intended to provide scientific understanding for the LCR rulemaking, but do not anticipate or prejudge those policy decisions.

2

Overview of Approaches

- Predict changes in children's blood lead levels (BLLs) using the Integrated Exposure Uptake and Biokinetic (IEUBK) Model
- Three age groups of interest:
  - 0 to 6 months of age
    - Average drinking water consumption rates and formula reconstituted with tap water since birth were evaluated
  - 1 to 2 years of age
    - Average drinking water consumption rate since birth were also evaluated
  - 0 to 7 years of age
    - Average drinking water consumption rates were evaluated

3

Overview of Approaches (cont.)

Approaches based on a modeled individual child include:

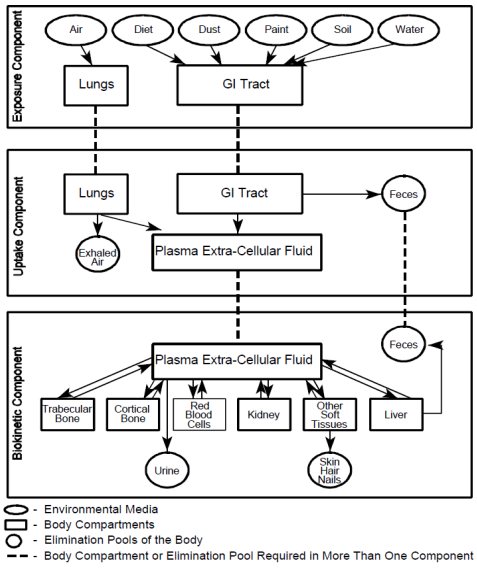
- Approach 1. Estimate the concentration of lead in drinking water that would result in a 1 or 5 percent increase in the probability of a child having an elevated BLL (EBLL).
- Approach 2. Estimate the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL.

Approaches based on a modeled population of children include:

- Approach 3. Estimate the amount of lead in drinking water that would result in a target population of children's predicted distribution of BLLs having the 95th or 97.5th percentile BLL of 3.5 or 5 µg/dL.
- Analysis also addresses different lead exposure scenarios including drinking water as the lone source of lead, and drinking water lead exposure in conjunction with other lead exposure pathways (air, food, soil and dust, and maternal contributions).

4

Structure of the IEUBK Model for Lead in Children



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Structure of the IEUBK Model for Lead in Children (cont.)

The IEUBK model uses **four** main components to mathematically and statistically link environmental lead exposure to children's BLLs:

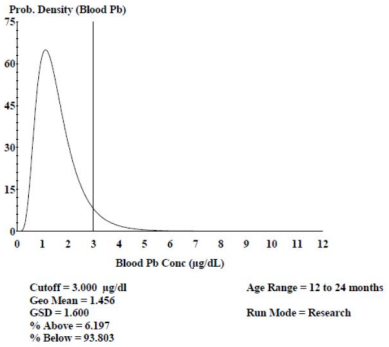
- **Exposures** are quantified by combining information on the concentration of lead in environmental media, the amount of contact with the media and the duration of the contact
- The **uptake** component models the transfer of lead to the bloodstream (i.e., the absorption) after intake into the child's body via the inhalation or ingestion routes.
- The **biokinetic** component consists of mathematical modeling of the movement of absorbed lead throughout the child's body, between the internal compartments and to the excretion pathways.
    - Modeling is done with consideration of the volume and weight of specific compartments of a child's body, as a function of age.
- **Variability** in children's BLLs is characterized by use of the lognormal probability distribution in the IEUBK model because children exposed to the same concentrations of lead in environmental media may have different BLLs due to differences in individual behavior, biology, and household characteristics

6

Background on the IEUBK Model

EPA OFFICE OF GROUND WATER AND DRINKING WATER

- Predicts BLLs in children from birth up until age 7
- Inputs and assumptions can be modified to explore changes in BLLs for specific sites/scenarios
  - E.g., lead in drinking water, soil, dust, air and diet
- Outputs are specific to an individual or a population of identically exposed individuals
  - Geometric mean BLL
  - Probability of exceeding a user-specified elevated BLL (EBLL)



7

Inputs to the IEUBK Model

- For this exploratory lead modeling effort, EPA modified IEUBK default inputs to reflect national level modeling and mimic SHEDS inputs
  - Allows for ease of comparison across model approaches and for use of most up to date, available, national scale data
- Three exposure scenarios for each age group:
  1. Drinking water (DW) lead exposures only
     - Concentrations of lead in all other media (e.g., soil, dust) set to zero
  2. *Geometric mean* soil and dust lead
     - Best central estimate values for all other non-DW lead concentrations
  3. *Arithmetic mean* soil and dust lead
     - Best central estimate values for all other non-DW lead concentrations

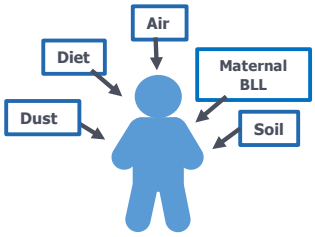
8

Inputs to the IEUBK Model Modified from Defaults

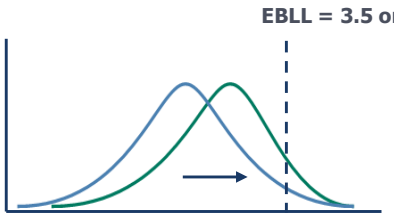
Variable	Input for This Analysis		Default in IEUBK
Air Lead (µg/m^3)	0.01		0.1
Soil Lead (mg/kg)	GM: 37	AM: 160	200
Dust Lead (mg/kg)	GM: 72	AM: 104	150
Diet Lead (µg/day)	0.27 – 3.29		2.26
Maternal BLL (µg/dl)	0.61		1
Mean Drinking Water Rate (L/day)	0.151 – 0.526		0.2 – 0.59
Soil/Dust Ingestion (g/day)	0.026 – 0.034		0.085 – 0.135
Geometric Standard Deviation	Infant: 1.45	Other: 1.6	1.6

9

Approach 1: Increased Probability of Elevated Blood Lead Levels for an Individual Child



Add Drinking Water Lead



Baseline Lead Exposure in IEUBK

What concentration of lead in drinking water increases the probability of EBLL in an individual child by 1% or 5%?

10

Approach 1: Results

Age Group	Exposure Scenario	Drinking Water Concentration (µg/L) Resulting in Specified Increase in the Probability of EBLL			
		EBLL = 3.5 µg/dL		EBLL = 5 µg/dL	
		1%	5%	1%	5%
0-6 Months	DW lead only	11.3	14.9	16.6	21.9
	Geometric soil/dust	8.2	11.7	13.4	18.7
	Arithmetic soil/dust	5.9	9.4	11.2	16.4
1-2 Years	DW lead only	26.5	37.1	38.5	54.1
	Geometric soil/dust	13.4	23.8	25.2	40.6
	Arithmetic soil/dust	8.1	18.2	19.4	34.7
0-7 Years	DW lead only	27.3	38.2	39.7	56.0
	Geometric soil/dust	12.9	23.6	25.1	41.1
	Arithmetic soil/dust	8.2	18.5	19.8	35.7

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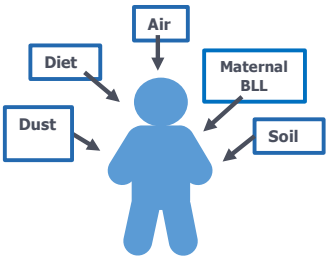
Approach 2: Incremental Change in Blood Lead Level for a Representative Child



Baseline Lead Exposure in IEUBK

Add Drinking Water Lead

What concentration of lead in drinking water increases the BLL of an individual child by 0.5 µg/dL or 1 µg/dL?

12

Approach 2: Results

Age Group	Exposure Scenario	Drinking Water Concentration (µg/L) Resulting in Specified Increase in Geometric Mean BLLs	
		0.5 µg/dL	1 µg/dL
0-6 Months	DW lead only	3.7	7.6
	Geometric soil/dust	3.8	7.7
	Arithmetic soil/dust	3.9	7.9
1-2 Years	DW lead only	11.1	22.5
	Geometric soil/dust	11.4	23.1
	Arithmetic soil/dust	11.5	23.4
0-7 Years	DW lead only	11.4	23.2
	Geometric soil/dust	11.7	23.8
	Arithmetic soil/dust	11.8	24.1

13

Summary of Approaches 1 and 2

- Results presented reflect the concentration of lead in drinking water that are predicted to result in specified unit changes in BLLs and increases in the probability of EBLLs.
- Results ranged from 3.7 to 56 µg/L with the lowest drinking water lead concentrations predicted for 0-6 month olds
- For Approach 1, the amount of drinking water lead concentration needed to increase the probability of EBLLs, decreases as background lead exposures increase
- For Approach 2, the amount of drinking water lead concentration needed to increase the geometric mean BLL, increases as background lead exposure increase

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Appendix F

EPA OVERVIEW OF APPROACH 3

Overview of the SHEDS-IEUBK Probabilistic, Population-Based Multimedia Exposure Modeling Analysis for Lead in Drinking Water

Drs. Valerie Zartarian, Jianping Xue, Rogelio Tornero-Velez, James Brown
U.S. EPA Office of Research and Development

External Peer Review of Proposed Modeling Approaches for a Health Based Benchmark for Lead in Drinking Water

June 27 28 2017, Washington, DC

Background

EPA/Office of Water (OW) requested Office of Research and Development (ORD) technical assistance in 2016 with exposure modeling to inform a "health-based benchmark" for lead in drinking water, in response to a NDWAC (National Drinking Water Advisory Council) recommendation regarding the revised Lead and Copper Rule.

ORD's approach is referred to as "Approach 3" for this external peer review.

2

Modeling Objectives

- To determine drinking water Pb concentrations that could keep specified percentiles of national blood lead level (BLL) distributions of different aged children below a defined benchmark BLL, for various scenarios
  - *using a probabilistic modeling methodology for a multimedia exposure analysis considering Pb in water, soil, dust, food, and air.*
- In addition, to evaluate the modeled predictions using CDC NHANES and other BLL data; to quantify relative contributions by each media/exposure pathway; and to identify key inputs.

3

Multimedia Exposure Modeling Approach to Inform a Health Based Benchmark for Lead

Applied EPA's SHEDS-Multimedia & IEUBK models to simulate aggregate Pb exposures and doses for different scenarios, to determine household tap water Pb concentrations that could keep BLLs below specified values.

- Developed methods to "couple" the models
- Compiled available data for model inputs
- Evaluated model estimates vs. measured BLLs (e.g., CDC NHANES)
- Identified key exposure pathways and factors via sensitivity analyses
- Addressed comments from a work-in-progress external peer consult
- Submitted paper to *EHP* journal; addressed external review comments

4

Overview of SHEDS-Multimedia

- **EPA/ORD's high-tier Monte Carlo human exposure model**
  - Accounts for variability in population exposures from multiple media based on realistic activity patterns, concentration distributions, and exposure factors (e.g. intakes)
  - Identifies key factors and relative contribution by exposure pathway for different ages/life stages and population percentiles
- **Scientifically defensible and transparent**
  - Comprehensive model evaluation with different chemicals
  - External peer reviews by EPA Scientific Advisory Panels (SAP)
  - >30 peer reviewed journal articles
  - Informed decisions for various pesticides and other chemicals
  - Code, documentation, and SAP materials on public website
  - Quality Assurance Project Plan for regulatory support applications

5

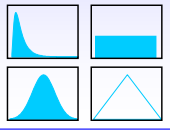
SHEDS-Multimedia Model Structure

Provides [ug Pb exposure/day] for IEUBK Coupling

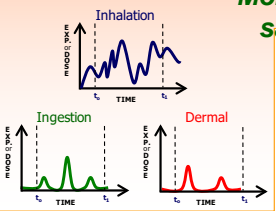
SHEDS outputs exposure distributions

Input Databases

- Activity Data: Census, NHANES, & CHAD diaries
- Media concentration distributions: Water, Soil, Dust, Food, Air, Surfaces
- Exposure Factor Distributions



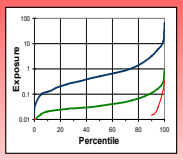
- Calculate Individual Exposure Profile



Monte Carlo sampling

Output

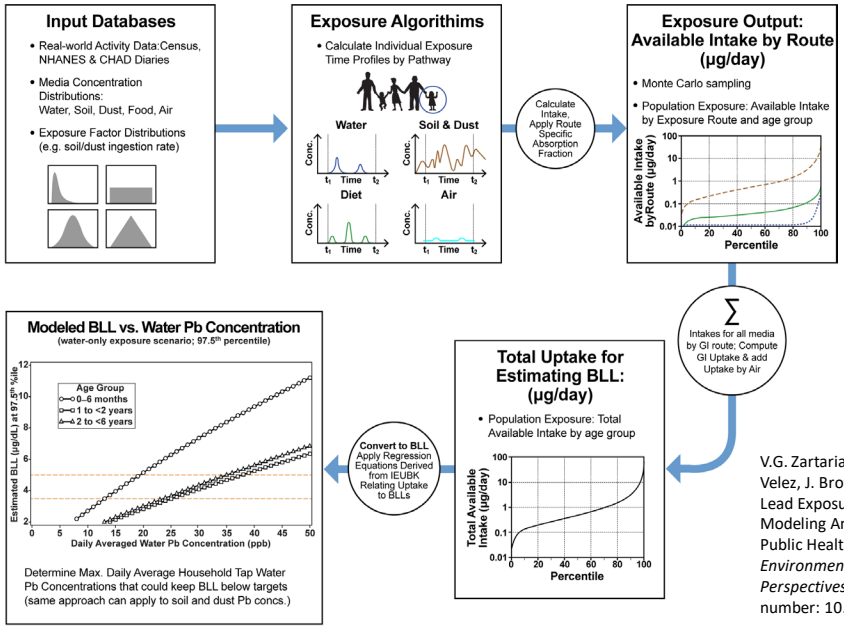
- Population Exposure (microgram per day)



SHEDS estimates age-specific probabilistic exposures (ug/day) that can be used as IEUBK exposure intakes.

6

SHEDS-IEUBK Pb Modeling Approach



V.G. Zartarian, J. Xue, R. Tornero-Velez, J. Brown, 2017, Children's Lead Exposure: a Multimedia Modeling Analysis to Guide Public Health Decision-Making, *Environmental Health Perspectives*, In Press, DOI number: 10.1289/EHP1605.

7

Summary of Response to Comments*

- ✓ Accounted for correlation of Pb in soil/dust & water
- ✓ Considered effects of exposure/dose averaging times and biological variability on estimates of population variability in blood lead
- ✓ Re-analyzed NHANES BLL data with 2 lognormal distributions to examine upper tail; stratified soil and dust Pb data by house age
- ✓ Conducted additional sensitivity analysis for soil/dust ingestion rate
- ✓ Clarified focus on national scale analysis for general U.S. population

*2016 Work-in-Progress Peer Consult, and *EHP* Journal External Peer Review Comments

8

Iterative Pb Modeling Process

2-day Baseline → 2-day with HUD and FDA data Evaluation improved

↓

2-day added correlated inputs and two distributions Further improved

↓

30-day added correlated inputs and two distributions Under-predicted GSD and relative errors increased

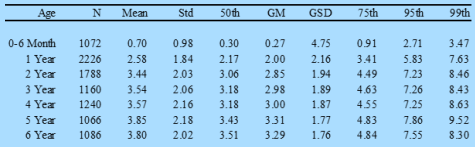
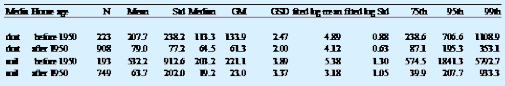
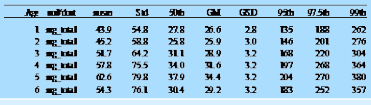
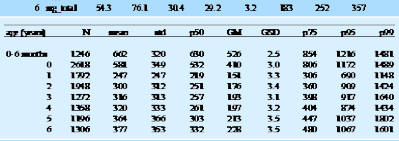
↓

The current modeling added biological variance Relative error 0-23%

9

Summary of Main Model Inputs

Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

Variable	Source	Values/Distribution Used
Dietary Pb Intake (ug/day)	Data from FDA Total Diet Study 2007-13 (TDS) & J Spungen, FDA-CSFAN unpublished data for recipe mapping; Method from Xue et al., 2010 *EHP*	
Soil and Dust Pb Concs. (ppm)	Empirical distribution from HUD AHHS 2005-2006 data http://portal.hud.gov/hudportal/documents/huddoc?id=AHHS_Report.pdf	
Soil/Dust Ingestion (mg/day)	Ozkaynak et al., 2011, *Risk Analysis*	
Water Consumption (ml/day)	NHANES 2005-20012	
Absolute Bioavailability	IEUBK Default	30% for soil&dust; 50% for water&food

Age	N	Mean	Std	50th	GM	GSD	75th	95th	99th
0-6 Month	1072	0.70	0.98	0.30	0.27	4.75	0.91	2.71	3.47
1 Year	2226	2.58	1.84	2.17	2.00	2.16	3.41	5.83	7.63
2 Year	1788	3.44	2.03	3.06	2.85	1.94	4.49	7.23	8.46
3 Year	1160	3.54	2.06	3.18	2.98	1.89	4.63	7.26	8.43
4 Year	1240	3.57	2.16	3.18	3.00	1.87	4.55	7.25	8.63
5 Year	1066	3.85	2.18	3.43	3.31	1.77	4.83	7.86	9.52
6 Year	1086	3.80	2.02	3.51	3.29	1.76	4.84	7.55	8.30

Media	House age	N	Mean	Std	Median	GM	GSD	5th	75th	95th	99th
dust	before 1950	223	207.7	238.2	103.3	133.9	2.47	4.89	0.88	238.6	706.6	1108.9
dust	after 1950	908	79.0	77.2	61.5	61.3	2.00	4.12	0.63	87.1	195.3	353.1
soil	before 1950	193	532.2	912.6	208.2	221.1	3.89	5.38	1.30	574.5	1841.3	5702.7
soil	after 1950	749	63.7	202.0	19.2	23.0	3.37	3.18	1.05	39.9	207.7	953.3

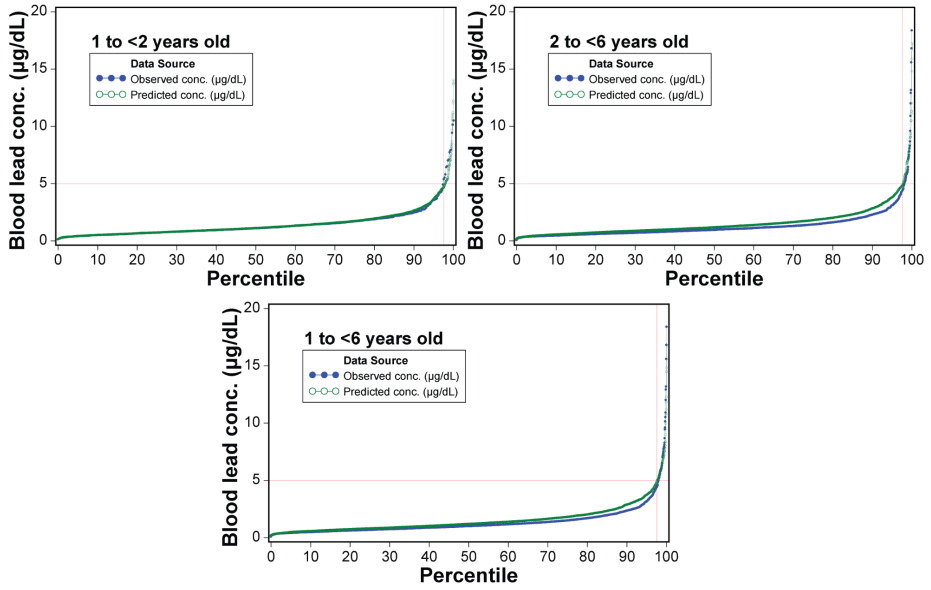
Age	soil/dust	mean	Std	50th	GM	GSD	95th	97.5th	99th
1	mg: total	43.9	54.8	27.8	26.6	2.8	135	188	262
2	mg: total	46.2	58.8	25.8	25.9	3.0	146	201	276
3	mg: total	58.7	64.2	38.1	38.9	3.2	168	220	304
4	mg: total	57.8	75.5	34.0	31.6	3.2	197	268	364
5	mg: total	62.6	79.8	37.9	34.4	3.2	204	270	380
6	mg: total	54.3	70.1	30.4	29.2	3.2	185	252	357

age [years]	N	mean	std	p50	GM	GSD	p75	p95	p99
0-6 months	1246	662	320	630	526	2.5	854	1216	1481
0	2681	588	349	582	480	3.0	806	1172	1459
1	1792	947	947	710	558	3.3	1106	660	1448
2	1048	800	382	751	676	3.4	1160	909	1424
3	1272	886	383	757	695	3.1	1198	917	1460
4	1358	820	333	801	697	3.2	1106	874	1454
5	1806	864	366	805	715	3.5	1147	1057	1602
6	1906	877	363	832	728	3.5	1180	1067	1601

10

Model Evaluation: SHEDS-IEUBK BLL vs. 2009-2014 NHANES BLL data

(30 day averaging time; addressing biological variability; 0—23% relative error)



Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

11

Model Evaluation: SHEDS-IEUBK BLL vs. 2009-2014 NHANES BLL data

(30 day averaging time; addressing biological variability; 0—23% relative error)

Age Group	Source	N	Mean	Std	50th	GM	GSD	95th	97.5th	99th	%>3 µg/dl
1 to <2 years old	Observed	475	1.47	1.30	1.12	1.16	1.92	3.60	5.54	7.90	6.95
	Predicted	3000	1.46	1.27	1.13	1.16	1.92**	3.58	4.60	6.41	7.70
	Relative Error		0%		1%	0%		1%	17%	19%	
2 to <6 years old	Observed	1892	1.33	1.60	0.98	1.03	1.89	3.13	4.39	7.15	5.44
	Predicted	3000	1.55	1.28	1.20	1.25	1.88**	3.84	4.94	6.67	8.60
	Relative Error		17%		23%	21%		23%	12%	7%	

N= sample size. GM = geometric mean. GSD = geometric standard deviation. Relative error is predicted minus observed, divided by observed. Absolute value of relative errors are shown here.

***Longitudinal (30 days) with correlated key inputs.**

****This GSD reflects the effect of exposure and biological variability on BLL.**

Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

12

Impact on Model Evaluation of Addressing Biological Variability

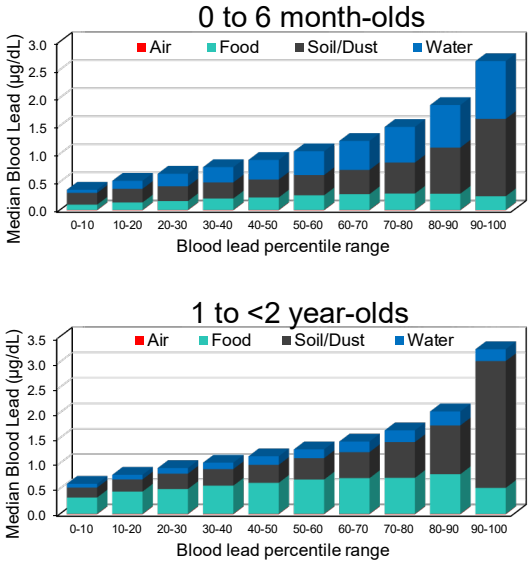
SHEDS-IEUBK model evaluation with 2009-2014 NHANES blood data*
(for U.S. children 1 to < 2 years old)

source	N	mean	Std	50th	GM	GSD	95th	97.5th	99th	% higher than 3 ug/dl
Observed	475	1.47	1.30	1.12	1.16	1.92	3.60	5.54	7.90	6.95
Predicted										
*	3000	1.33	0.88	1.11	1.16	1.64	2.95	3.75	4.88	4.87
**	3000	1.46	1.27	1.13	1.16	1.92	3.58	4.60	6.41	7.70
relative error										
*		9%		1%	0%	15%	18%	32%	38%	
**		0%		1%	0%	0%	1%	17%	19%	

longitudinal (30 day averaging time) with correlated key inputs
* = without accounting for biological variability; ** = with adding biological variability

13

Modeled [illegible]
(30 day averaging time; ac[illegible]

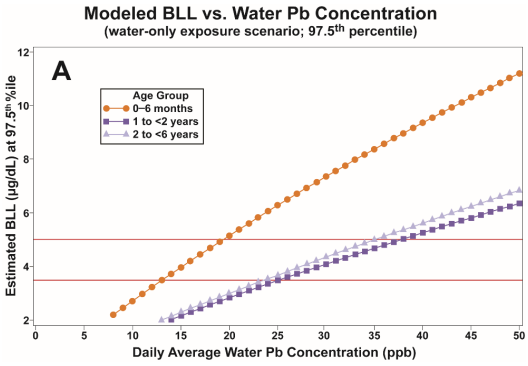


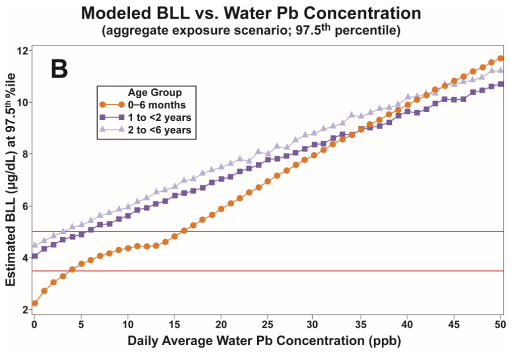
- For higher percentiles, soil/dust ingestion is the major pathway.
- Water ingestion is also an important contributor, especially for infants.
- Food Pb is a background contributor.
- Inhalation contribution is small.

Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

14

Determination of Drinking Water Pb Concentrations that Could Keep Children's BLL Below Specified Targets





Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

15

SHEDS-IEUBK results for Max. Daily Average* Household Tap Water Pb Concentrations that Could Keep BLL Below Specified Values

30-day averaging time; accounting for correlations, biological variability, other feedback

Age Group	Exposure Scenario	BLL 3.5 µg/dL @ 97.5th %ile	BLL 5 µg/dL @ 97.5th %ile	BLL 3.5 µg/dL @ 95th %ile	BLL 5 µg/dL @ 95th %ile
0 to 6 months old	Water Only	13.1 ppb	19.3 ppb	14.1 ppb	20.8 ppb
	Aggregate	3.7 ppb	15.8 ppb	6.9 ppb	17.4 ppb
1 to <2 years old	Water Only	25.1 ppb	37.7 ppb	30.9 ppb	46.0 ppb
	Aggregate	-	5.4 ppb	2.5 ppb	14.2 ppb
2 to <6 years old	Water Only	23.6 ppb	35.0 ppb	29.4 ppb	43.6 ppb
	Aggregate	-	2.8 ppb	1.1 ppb	12.1 ppb
0 to 7 years old	Water Only	20.1 ppb	29.5 ppb	27.3 ppb	41.0 ppb
	Aggregate	-	4.7 ppb	2.2 ppb	12.9 ppb

- **Daily avg. of a distribution reflecting real-world monitoring scheme TBD*
- *"-" means BLL will not be below targets even with 0 ppb Pb in water*

Zartarian et al., *EHP*, In Press, DOI: 10.1289/EHP1605.

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Strengths and Limitations of SHEDS-IEUBK_Pb Modeling Approach

Strengths

- Represents an advance in science
  - SHEDS-Multimedia & IEUBK are published, evaluated models
  - Population-based, probabilistic, multimedia approach enhances understanding of relationship between Pb in drinking water and BLLs
  - Uniquely reports percent contribution to children's BLL by exposure pathway, population percentile, and age group
  - Sensitivity analyses identify key factors, media, and exposure pathways
  - SHEDS-IEUBK estimates compare well against CDC NHANES BLL data
  - Approach can be applied to other environmental media to inform decision-making considering exposures aggregated from multiple media
- Reflects scientific input from external peer reviewers

Limitations

- Requires selecting a BLL benchmark; CDC reference level may change
- Requires detailed input data (e.g., distributions rather than point estimates)
  - Uncertainties and limitations in data for key variables
- Currently intended for national scale analyses

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Acknowledgments

- EPA/Office of Research and Development (ORD) managers for providing guidance and review
- EPA/Office of Water and other EPA Program Office staff, and other ORD scientists for technical input
- ORD contractors for assistance with model inputs
- Versar, Inc. and external reviewers

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Appendix G

PUBLIC STATEMENTS

Public Comment 1

Tom Neltner
Chemicals Policy Director, Environmental Defense Fund

My name is Tom Neltner and I am with the Environmental Defense Fund. Thank you for your time and for EPA's excellent presentation.

This is an important outgrowth of the discussion that occurred in the Lead and Copper Rule Working Group, where we realized there was a level at which the public health community needed to be aware of lead in drinking water so it could do what it does best: investigate it, work with the utility, and work with the community. This was not an attempt to define a safe level for lead—that level is zero for water (the Maximum Contaminant Level Goal [MCLG] is zero). It was a level designed to trigger public health investigation, largely modeled after a Housing and Urban Development (HUD) rule, which said that if a Section 8 Housing Choice Voucher landlord becomes aware of a child with an elevated BLL, they need to investigate. That rule provides a notice to the public health community/local health department to investigate.

The purpose of the lead in drinking water level is to give parents, doctors, and the public health community information so they can make decisions about that child. The Lead and Copper Rule Working Group chose the most vulnerable group (the child dependent on infant formula). I appreciate EPA's efforts and outstanding analysis to go beyond what the Lead and Copper Rule Working Group asked for.

The relative source contribution chart at the end provides great context to understand and put drinking water in some appropriate context for one-year-olds. Also, this was apparently the first time that dietary intake exposure has been done in about 20+ years. The dietary intake exposure work provided really useful information that also has other purposes.

The key here is to try to identify, develop, and use the best models. I appreciate you being here and your work.

Public Comment 2

Warren Friedman, Ph.D., CIH, FAIHA
Senior Advisor to the Director, Office of Lead Hazard Control and Healthy Homes,
U.S. Department of Housing and Urban Development

My name is Dr. Warren Friedman and I am Senior Advisor with the Department of Housing and Urban Development (HUD). Thank you for the opportunity to provide public comments on this important lead modeling effort. A standard disclaimer, the views reflected in these comments are my own and do not necessarily represent HUD's policies, strategies, or opinions.

Thanks also to the EPA staff for putting HUD's work on its American Healthy Homes Survey (AHHS, cited in the report) from 2005-2006 (one of three lead-in-housing surveys HUD has conducted) to use in this effort, as Dr. Zartarian has noted, by using AHHS dust-lead and soil-lead data in the draft report.

The draft's use of 1950 vs. 1978 as a housing year of construction "cut point to identify homes with likely sources of lead-based paint," as described in Appendix Section A.2.1, is reasonable for this modeling based on AHHS data. It is even more appropriate as a cut point to identify homes with lead-based paint hazards, as these are defined by EPA's Office of Pollution Prevention and Toxics (OPPT) (40 CFR 745.65). Using data from the published 1960 and 1978 cut points in AHHS, 76% and 52% of pre-1960 homes had lead-based paint and lead-based paint hazards, respectively, while significantly lower percentages, 35% and 22% of pre-1978 homes, had lead-based paint and lead-based paint hazards, respectively. Using data from the published 1940 cut point shows that these older pre-1940 homes had even higher percentages of lead-based paint and lead-based paint hazards, 86% and 67%, respectively. As a result, the 1950 cut point chosen is reasonable considering its focus on homes, high fractions of which have lead-based paint and/or lead-based paint hazards, while including a larger fraction of the housing stock underlying the estimates than would be the case if only pre-1940 homes were used.

One issue worth noting concerns a process described in the draft report's Section 5.7. The draft accurately states that "Dust wipe samples were measured in AHHS as dust lead loading levels ($\mu g/ft^2$), rather than dust lead concentrations ($\mu g/g$), which is the figure appropriate for input into the IEUBK model." This required EPA to convert dust lead loading levels into dust lead concentrations empirically. The conversion model used is from EPA's "Lead: Human Exposure and Health Risk Assessments for Selected Case Studies" report from 2007 (cited in the draft), which does not give quantitative precision or uncertainty measurements for the coefficient of these regression equations. As noted in the 2007 report's Appendix G, in Section G.3.4 on the General Urban Case Study, however, "this conversion introduces considerable uncertainty into the dust model." The effect of this uncertainty on the current modeling effort should be assessed carefully. As Dr. Hafez noted earlier, alternative IEUBK inputs could be used. The assessment of alternatives need not be just statistical, but could be methodologic as well, regarding the use of dust-lead concentrations in IEUBK to address a lead-in-housing exposure when EPA's OPPT uses dust-lead loading to define dust-lead hazards in target housing.

Thank you.

Public Comment 3

Douglas Crawford-Brown, Ph.D.
Director, Cambridge Science and Policy Consulting

Thank you to the panel. My name is Dr. Douglas Crawford-Brown and I am Professor Emeritus at the University of North Carolina, but that moved 12 years ago to the University of Cambridge, and I am now a resident of California.

I have three quick comments. To preface that, I am fully supportive of EPA's modeling effort and thank you to Dr. Zartarian for the update on the Environmental Health Perspectives (EHP) paper results, which addresses some of the issues I am raising.

One point has to do with the fact that all of the approaches currently are set up with the idea that there is a 'risk cup', and water pushes one over the lip of the cup. I would like to see that turned upside down and begin to ask what happens if we remove lead from water, what happens if we remove it from air, what happens if we remove it from food, and so forth. That is a different kind of analysis, but EPA very nicely has set up the models so that they can be turned in either of those two directions.

The second issue has to do with this biological averaging time. I think one has to look back at the epidemiological and clinical data to see what sort of biological averaging time is relevant to those data. Those data don't deal with 2-day or even 30-day averaging. The only reason I raise that issue is that under the current Lead and Copper Rule spot samples that are taken, and therefore there is a danger that this new health-based benchmark (if there is a new health benchmark) will become what the spot samples are compared against. The spot samples are not relevant to this kind of long-term health effect.

The last issue, which Dr. Zartarian spoke to, has to do with truncation and correlation of the parameter values. Those are not well-developed in many cases right now. If you remember slide 10, those cumulative distribution functions are quite steep once you get out past the 95^{th} percentile. The question then becomes, is there a percentile where it is reasonable to try to estimate what the percentage of people would be. I would say that 97.5^{th} percentile is a bit pushing it, given what we currently know.

In response to a question from the facilitator, Dr. Brown clarified that the American Water Works Association (AWWA) sponsored his attendance to this public meeting, but he takes responsibility for his comments.

Public Comment 4

Lindsey Jones, M.S.
Senior Toxicologist
Toxicology Division, Texas Commission on Environmental Quality

Good afternoon, my name is Lindsey Jones, and I am a toxicologist with the Texas Commission on Environmental Quality (TCEQ). I appreciate the opportunity to speak to you about the Environmental Protection Agency's (EPA's) "Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water" document. My comments to you today provide an overview of the TCEQ's written comments to the EPA, which include more detailed information and supporting citations.

We first strongly encourage you to guide the EPA away from using the term "health-based benchmarks." The EPA states that this term is used to avoid confusion; however, use of the term only causes further ambiguity due to the fact that the benchmarks are actually based on a modeling exercise, as opposed to the existing health-based risk assessment framework. At a minimum, the EPA should be using a more accurate descriptor, such as a household screening level. We also caution against tying an action level to an ever-moving target such as the 97.5th percentile of the U.S. childhood blood lead level distribution. This level does not accurately communicate the risk of possible adverse health effects to the general public and will quickly be out of date due to shifts in the population and the ever-decreasing blood lead concentrations. A constantly moving action level results in regulatory uncertainty for long-term environmental projects and distrust from the public and local governments.

In the absence of deriving a true health-based benchmark, the TCEQ encourages the panel to focus on Approach 1, and on estimating the concentration of lead in drinking water that corresponds to a 5% increase in the probability of a blood lead level above 5 µg/dL. This is consistent with the EPA's historical approach for assessing lead exposure and the use of a more stringent (yet reasonable) probability criterion that may be used by EPA for more serious health effects. In addition, the TCEQ recommends that the EPA use the 37/72 µg/g (ppm) geometric mean background soil/dust lead concentrations. The resulting drinking water concentration provides the protection recommended by the National Drinking Water Advisory Council.

Finally, the TCEQ recommends that the panel give the soil ingestion, soil/dust concentration, and outdoor air input parameters an appropriate level of scrutiny. Various analyses in the draft report as well as Appendix A incorporate higher-end exposure inputs, rather than inputs that are more representative of typical lead childhood exposure. For example, EPA's draft report uses a mean soil concentration of 160 µg/g (ppm; Exhibit 7) based on the American Healthy Homes Survey (AHHS), while Table 7-2 of the AHHS shows that the mean for southern states actually ranges from 67-83 ppm with a 95% confidence interval upper bound of 91-109 ppm (US HUD, 2011)[1].

Thank you for your consideration and the opportunity to provide these comments.

[1] U.S. Department of Housing and Urban Development. 2011. American Healthy Homes Survey; Lead and Arsenic Findings. Office of Healthy Homes and Lead Hazard Control. Accessed on August 4, 2017. Available at: https://portal.hud.gov/hudportal/documents/huddoc?id=AHHS_REPORT.pdf

Appendix H

REVIEWER POST-MEETING COMMENTS[1]

[1] This appendix provides post-meeting comments for the seven reviewers (all except Dr. Prévost) who provided written comments to ERG after the meeting.

COMMENTS SUBMITTED BY

Panos Georgopoulos, Ph.D.

External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

The selection of the three life stages (0-6 months, 1-2 years, and 0-7 years) for the modeling analysis represents a reasonable compromise given the limitations in available data and in the formulation of the models (particularly IEUBK) that were used. Increasing the temporal resolution of the life stages modeled would in principle be feasible (though not straightforward) via the incorporation of available physiological and exposure factor information (of course, the latter would still have substantial data gaps). However, it does not appear that corresponding clinical and epidemiological data are available at such resolution to justify the effort required by a more "temporally refined" analysis. It would be very useful however to "break" the 0-7 years life stage in a way that would differentiate pre-school and school years (as the exposure patterns of the child change substantially with its introduction in the school environment). Future studies (that would require development and application a "next generation" IEUBK-type extended model) should consider explicitly *in utero* exposures (that may be critically important for neurodevelopmental effects) by incorporating the appropriate life stages for both the mother and the fetus (in a combined mother-fetus PBPK model formulation). Since this option is not currently available, this recommendation is relevant not only to life stage selection but to modeling needs that should be eventually addressed. At this point it should be reminded that IEUBK has been formulated and applied as a model appropriate for considering exposures representative of each year of the child's life and not for considering relatively short-term and transient exposures. In the past, the standard recommendation for applying IEUBK has always been that "exposures must be for ≥1 day/week for 90 consecutive days"; however, the modeling effort under review adopts a 30 day period for its analysis under Approach 3, a matter that needs further explanation and justification (beyond the reference currently provided in the technical document describing the modeling effort under review).

Regarding the strengths and weaknesses of the modeling scenarios conducted, these can - and should - only be evaluated specifically in the context of the modeling approaches that employed these scenarios. The strengths and weaknesses of the different modeling approaches are the subject of Question 3 and are discussed in the response to that question (though in this reviewer's opinion, discussion/evaluation of the modeling framework and modeling approaches should logically precede the discussion of the scenarios used).

Nevertheless, it should be pointed out here that Approaches 1 and 2 appear to be using the premise that applying IEUBK with input values that represent measures of central tendency (such as the geometric mean) for various exposure-related variables/parameters of the model, would produce corresponding outputs that also represent measures of central tendencies of distributions of these outputs for subpopulations with the

aforementioned variabilities in exposure factors. This is not justifiable and requires re-evaluation of the relevance and interpretation of the scenarios employed in Approaches 1 and 2, including those considering water-only exposures, which represent an "extreme" situation (and rather implausible beyond the infant life stage) that is more relevant to a model sensitivity analysis. Approaches 1 and 2 present interesting case studies but in fact they reflect the biokinetic responses to specific exposure scenarios that are not generalizable to the population of concern (all children in the US or even children within a population represented by the NHANES sample considered in the application of Approach 3).

On the other hand, Approach 3 employs a probabilistic methodology for assessing aggregate exposures via the SHEDS model; this approach is scientifically sound with respect to exposure characterization (though the coupling with a regression-based equation representing IEUBK outputs requires further discussion) and the scenarios modeled using this approach are relevant to "real world" situations and furthermore conform with current practices for multimedia/multipathway exposure and risk characterization.

Though the levels of the two target BLLs considered are appropriate, there is concern as to whether the parameterizations of the models (even for Approach 3) are appropriate for calculations at the upper tail percentiles of the exposure distribution (where lognormality assumptions may not be valid). Though this is not an alternative scenario per se, it might be useful to consider order statistics (or "statistics of extremes") for distributions of the upper tail percentiles of observed BLLs and compare those with upper percentiles resulting from distributional (probabilistic) model calculations.

Furthermore, it should further be emphasized that the scenarios involving NHANES (and NHEXAS) populations and corresponding exposure-relevant factors produce as outputs exposure distributions (and corresponding upper percentile estimates) that are strictly relevant to these populations and not to the US population (which includes potentially highly exposed subpopulations as well as sensitive subpopulations that are not "captured" in the NHANES samples). The Approach 3 scenarios that are presented in the document under review were indeed simulated (and found to perform in a satisfactory manner) with inputs that are appropriate and relevant for the populations considered. It would be very informative to consider and perform scenarios that consider inputs not limited to those relevant to the NHANES (or NHEXAS) populations but instead use inputs (e.g., water consumption rates from US EPA's Exposure Factor Handbook) that apply to the distributions of the overall US population and compare the output distributions (not only central tendency measures and selected upper percentiles) with those derived for the NHANES population (using NHANES water consumption rates). It would also be very informative to run selected scenarios for the populations of different climate/ physiographic regions of the US and compare the effect of different exposure factors (as different climate/ physiographic regions, such as e.g. the northeast vs the southwest, also have different soil properties, housing characteristics, indoor/outdoor activity patterns, etc.).

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

Though model inputs are generally reasonable, what matters is the context in which they are used and the interpretation of the outputs they produce. As was mentioned in the response to Question 1, applying IEUBK with input values that represent measures of central tendency (such as the geometric mean) for various exposure-related variables/parameters of the model, does not necessarily produce corresponding outputs that also represent measures of central tendencies of distributions of these outputs; this is important when trying to interpret the outcomes from Approaches 1 and 2. However, even in the distributional/ probabilistic application employed in Approach 3, it is not clear how all the, potentially significant, correlations between exposure-relevant input parameters are taken into account. These correlations are expected to be especially significant for the most highly exposed individuals within the population simulated, and therefore to affect the upper tail percentiles (95% and 97.5%) that are derived in Approach 3. SHEDS can employ a "bottom up" approach that assembles individual information from databases to build empirical distributions of exposure factors that could capture correlations if appropriate sampling rules are used. However, the descriptions of "Inputs for IEUBK-SHEDS Coupled Analysis," in Exhibits 13-20 (pages 33-40 of the document under review) refer to the empirical distributions summarized in Exhibits 4-10 (pages 21-30 of the document), generally without providing information on how correlations are treated. There are certain statements, such as "in SHEDS the input for time spent outdoors also impacts the soil and dust ingestion rate, as well as soil and dust exposure," on p. 22 of the document, but it is not clear how this impact - especially on the rate, rather than on the cumulative intake - is quantified in the calculations. On the other hand, on p. 27 of the document, explicit information on correlations used in modeling inputs is provided: "In conducting the SHEDS-IEUBK approach 3 analysis for soil lead concentration, an empirical distribution was fit to data provided by HUD from AHHS (HUD, 2011). The data were stratified and weighted by house age pre- and post-1950, and a correlation coefficient of 0.48 between dust and soil lead concentrations was assigned in SHEDS. A correlation coefficient of 0.2 was also applied to the water and dust concentration distributions, based on EPA's NHEXAS study Clayton, Pellizzari, Whitmore, Perritt, and Quackenboss (1999)." Given the importance of correlations on results corresponding to the extremes/tails of the output distributions, it is recommended that all correlation rules used in the SHEDS-IEUBK simulations are explicitly listed and summarized in a table.

However, there is still a variety of other issues with data limitations. One example is that contributions to lead levels in water from distribution system service lines versus premise plumbing are not separated. Another example involves the use of dust lead concentration inputs from AHHS mentioned in the previous paragraph of the present response, in relation to dust/soil lead correlations; specifically, on p. 26 of the document it is stated that: "[o]f the 5,612 floor dust wipe samples taken during the survey, only 404 were above the detection limit of 5 µg/ft2. However, raw analytical data files were obtained by HUD from the laboratory processing the floor wipes, which included some of the samples below the level of detection, resulting in 1,131 dust wipe samples with data available to calculate dust lead levels. These additional data points were used by HUD in the calculation of the mean values for dust lead from floor wipes. According to HUD, "this procedure provides unbiased estimates of means, provided that measurements below the detection limit are normally distributed about the true value of the analyte, as is generally assumed in discussions of the detection limit" (HUD, 2011, p. 43)." The statement from the AHHS report (HUD, 2011, p.43) that is provided in quotes in the document under review, is actually attributed to the first edition of the textbook by Helsel (2005); however, this assumption of normality is not necessarily used in the treatment of non-detects in other modeling inputs in the present effort currently under review (and is a potentially important issue, as the actual percentage of samples above detection limit is only around 7%). Furthermore, the fact,

quoted on p. 27 of the document under review, that "dust lead concentration is assumed to be correlated with soil lead concentration and that both tend to be highly variable in different areas of the United States" points (as mentioned in the response to Question 1) to the potential usefulness of performing and comparing simulations for specific physiographic etc. regions of the US. Finally, another example of problematic inputs (or data gaps that can affect outcomes) can be found on p. 28: "Zero- to 6-month-olds and 0- to 1-year-olds were assumed to have the same soil and dust ingestion rate as 1-year-olds due to lack of data."

It should be mentioned that various input data limitations are indeed explicitly recognized and discussed in the document under review. For example, on page 50 it is stated that "there are limitations and uncertainties with some of the inputs associated with both the IEUBK and SHEDS model" and that specifically "there is a limitation in using point estimates for the absorption fraction of lead from the different environmental media." However, the values used are consistent with what is currently used in the IEUBK model. Further, there is no drinking water intake value specific to formula-fed infants in the NHANES data that are used in SHEDS, and therefore the population that the NDWAC suggested considering is not explicitly considered in this approach. It is also unclear the extent to which the underlying distributions in the SHEDS model, as well as the NHEXAS-derived correlations between distributions in the SHEDS model, are accurate representations of those found in the U.S. population." Such discussions within the document under review are indeed useful; the USEPA should consider summarizing/organizing such points (involving data limitations and gaps) either in stand-alone tables or in additional columns of the tables ("Exhibits") describing the modeling inputs.

It appears the NHANES water consumption data have been used for the input distribution of water consumption rates, instead of the (substantially different) distributions provided in USEPA's Exposure Factors Handbook, in order to allow comparisons of SHEDS-IEUBK BLL outcomes with NHANES BLL levels. As recommended earlier, in the response to Question 1, it would be very useful to perform SHEDS-IEUBK simulations and compare calculated BLL outcomes using EFH water consumption rates to those calculated using NHANES water consumption rates.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

- **a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.**
- **b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.**
- **c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated**

BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

The IEUBK User's Guide (2007) states, regarding the distribution calculated by the model, that "the plausible range reflects predicted variability among individuals with the same exposure scenario, and should not be confused with a statistical confidence limit (which is a measure of statistical uncertainty in a predicted value such as a geometric mean)" and that "the estimated probability of exceeding the specified PbB level of concern, corresponding to the given exposure scenario or scenarios (for multiple runs in a given medium)" can be interpreted in the following two ways:

1. The output of the model may be considered to be the best estimate of a plausible range of PbB concentrations for a hypothetical child under a specific Pb exposure scenario. The range of values is centered on the geometric mean PbB concentration expected for a typical child with this exposure scenario. The portion of the upper tail of the probability distribution exceeding some chosen PbB level of concern provides an estimate of the risk of exceeding that level for a typical child of that age residing in the same household and with the same exposure history.

2. The output of the model may also be considered to be the predicted geometric mean PbB of a population of children under the same Pb exposure scenario. That portion of the upper tail that exceeds some chosen PbB level of concern indicates the fraction of the population exceeding that level when all of these children have the same exposure history.

The IEUBK User's Guide (2007) also states that "[a] common misinterpretation of IEUBKwin is that it predicts community geometric mean PbB and the fraction of the population of children at risk when the input is the mean or geometric mean of household-specific environmental Pb concentrations. That misinterpretation arises, particularly when the environmental variables have a wide distribution among the neighborhoods of the community. A correct approach requires applying the model to each individual home (or area with homogeneous lead concentrations) and combining these results as an aggregate to form an estimate of neighborhood or community risk."

Given the above statements, it can be claimed that the proper way of deriving a distribution of BLLs using IEUBK – and presenting the corresponding outputs, as per charge Question 3.a - is in fact the one provided by Approach 3. As mentioned in the responses to previous questions, Approaches 1 and 2 represent interesting case studies, but the results presented are not generalizable to any real population of concern.

Approach 3 employs a probabilistic/distributional approach, implemented in a state-of-the-art exposure model, SHEDS. The document under review states (on p. 18), regarding SHEDS: "Several features of SHEDS contribute to making it a unique and powerful tool. First, since the model uses a time-series approach for simulating dietary and residential exposures, SHEDS accounts for variability that arises from separate activities or eating occasions. The model also uses two-stage Monte Carlo sampling, which allows variability in population exposure and dose estimates and uncertainty associated with different percentiles to be quantified. [... ...]. In addition, SHEDS-Multimedia can account for correlated inputs." The above statement is factually correct; however, it can be misleading in the context of the present effort, as not all mentioned

features of SHEDS are used in the application currently under review. For example, two-stage Monte Carlo sampling is not used: only variability associated with exposure factors is explicitly considered via Monte Carlo; biological variability is "lumped" in the GSD used in conjunction with IEUBK (linked with SHEDS) and uncertainty is not treated. This is in fact discussed on p. 60 of the document under review: "uncertainties in this analysis are the model averaging time, and how the coupled models capture biological and other sources of variability in the geometric standard deviation of BLLs. The latter issue relates to model coupling for this analysis. SHEDS-Multimedia estimates reflect exposure variability, but not biological variability or other sources of variability such as measurement or model error. Because IEUBK blood lead estimates do not reflect inter-individual behavioral and pharmacokinetic differences, a GSD of 1.6 is applied to outputs of IEUBK to account for biological variability and measurement error, but does not account for exposure variability. Outputs from the coupled SHEDS-IEUBK models, therefore, need a variability factor to account for the GSD difference between modeled and measured BLLs and reflect real-world BLLs that also account for biological variability." The use of this "extra" variability factor should be only considered an "interim solution" for the present application; it is strongly recommended that future work on the matter explores the feasibility of accounting for inter-individual variability via standard methods currently used in pharmacokinetic modeling practice such as Nonlinear Mixed Effects Modeling (NONMEM; see, e.g., Owen and Fiedler-Kelly, 2014; Wang, 2015).

In any case, it should be noted that though SHEDS is a state-of-the-art probabilistic model, that has been continuously evolving and refined over the past two decades, IEUBK is a well-tested but now rather old tool (developed in the 1990s with data from the 1980s) that does not incorporate many recent developments in physiologically-based pharmacokinetic modeling and systems biology of exposures. It cannot account for episodic exposures (traditionally it has been applied for a minimum of 90 day periods over which exposures are taking place, though the current application considers 30day exposures for the SHEDS-IEUBK simulation), it cannot account for changes in physiological parameters due to activity, etc. and it considers childhood life-stages in year-length periods. There are many factors that affect lead exposure biology that cannot be dealt with IEUBK. For example, co-exposures to other contaminants may affect prenatal and postnatal Pb toxicokinetics and toxicodynamics (see, e.g. Sasso et al. 2010; Boucher et al. 2014) while gender-related differences in exposure patterns and in the toxicokinetics of absorption, metabolism and excretion of Pb may account for gender-differences in Pb toxicodynamics and in Pb neurotoxicity (e.g. Mushak 2011; Senut et al. 2012; Vahter et al. 2007; Sen et al. 2015). In the future USEPA should consider either extensively updating IEUBK or adopting a PBPK formulation that extends, with variable temporal resolution over multiple lifestages and includes pregnancy/gestation with coupled mother/fetus models to account for *in utero* exposures.

From a more short-term model implementation/coding perspective, an issue that should be addressed in the near future is the lack of flexibility in incorporating explicit input variability when using the "batch mode" of IEUBK (compared to the options available when using the "standard mode" of IEUBK, via the guided user interface windows, as discussed on p. 59 of the document under review. Implementing a more flexible "batch mode" could facilitate the "direct" coupling of SHEDS with IEUBK (i.e. instead of using a regression fit of IEUBK outputs) and even performing stand-alone (probabilistic) Monte Carlo applications of IEUBK. The current application utilized a polynomial regression fit of IEUBK solutions as a "fast equivalent operating model (FEOM)" closely approximating numerical IEUBK solutions via an algebraic formula. (Nevertheless, the

exact range of applicability of any such "FEOM" must be explicitly identified and documented, in order to avoid any potential future "misuse" of the formulation outside this range.)

Regarding Question 3.c, this reviewer would strongly recommend to use Approach 3 directly (instead of using it to address the questions of Approaches 1 and 2).

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

The responses to the previous questions have already described the reasons Approach 3 provides a more comprehensive and scientifically defensible framework that can calculate BLLs for direct comparison with existing (NHANEs and NHEXAS) blood lead data. NHEXAS offers the additional potential advantage that individual-specific exposure information can be linked to biomarker (BLL) data, while this potential is generally not associated with NHANES data. On the other hand, the "magnitude and continuity" of the NHANES database make it the "gold standard" for evaluating modeling predictions. However, as repeatedly mentioned in the responses to the previous questions, the existing blood lead data are only representative of the population (e.g. NHANES) sampled and do not reflect a distribution of the US population. In any case, agreement of probabilistic/distributional model predictions with corresponding existing (NHANES, NHEXAS) blood lead data builds confidence to the model and justifies (with recognition of the appropriate caveats) its application to ranges beyond those corresponding the aforementioned databases.

Both "local" and "global sensitivity analysis" can (and should) be utilized in gaining a better understanding of the key inputs and parameters affecting the outputs of IEUBK, SHEDS and of their combined application. Local sensitivity analysis involves multiple perturbations around a nominal point of the model's response surface, while global refers to sensitivity analysis across the entire response surface (see, for example, page 71 of USEPA, 2009, Guidance on the Development, Evaluation, and Application of Environmental Models, EPA/11/K-09/003; also, any standard reference, such as, e.g. Saltelli et al. 2004 or Saltelli et al. 2008). It is recommended that, for the application currently considered, at a minimum a systematic set of One-at-A-Time (OAT) sensitivity calculations are performed. OAT calculations are the "most tractable" sensitivity calculations, as they select a "base case set" of input values and perturb each input variable by a given percentage away from the base value while holding all other input variables constant. Such sensitivity calculations yield "biased" local measures of sensitivity (no matter how "large" or "small" a perturbation they consider), that depend on the choice of base case values. One way to avoid this bias is to use the "Morris's OAT" scheme for screening purposes because it is a relatively simple global sensitivity analysis method: it "entails computing a number of local measures (randomly extracted across the input space) and then taking their average" (see, e.g. USEPA, 2009). So, Morris's OAT provides a measure of the importance of an input factor in generating output variation, and while it does not quantify interaction effects, it does provide an indication of the presence of interaction (see, e.g. Wainwright et al., 2014). It is strongly recommended that the work under review considers employing a global sensitivity analysis such as, specifically, Morris's OAT. OAT can provide useful insights for IEUBK modeling. In the case of SHEDS, with proper sampling (and maybe with certain code modifications) the Monte Carlo simulations can provide

sufficient response information for the entire sampling space of the variable of concern, that can also allow the construction of global sensitivity metrics.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

In this reviewer's opinion, improvements should focus on Approach 3, which is the most scientifically defensible and has the potential of explicitly accounting for variability (including variability of drinking water concentrations measured at homes during sampling) and uncertainty via the two-stage Monte Carlo framework built in the SHEDS model.

Both variability and uncertainty can (and should) be addressed in a two-stage Monte Carlo approach. Chapter 2 of USEPA's Exposure Factor Handbook (USEPA 2011) states (on page 2-1) that "[P]roperly addressing variability and uncertainty will increase the likelihood that results of an assessment or analysis will be used in an appropriate manner. Characterizing and communicating variability and uncertainty should be done throughout all the components of the risk assessment process (NRC, 1994). [...] Proper characterization of variability and uncertainty will also support effective communication of risk estimates to risk managers and the public. [...] U.S. EPA (1995), following the NRC (1994) recommendation, has advised the risk assessor to distinguish between variability and uncertainty." The same USEPA document (EFH, on page 2-5) describes the four-tier approach of the International Program on Chemical Safety (WHO, 2006) for addressing uncertainty and variability, that is also consistent with USEPA practices and recommendations: The four tiers include "the use of default assumptions; a qualitative, systematic identification and characterization of uncertainty; a qualitative evaluation of uncertainty using bounding estimates, interval analysis, and sensitivity analysis; and a more sophisticated one- or two-stage probabilistic analysis." Although SHEDS provides these options, the application currently under review does not explicitly address uncertainty; this should be addressed in any future work on this matter.

Responses to previous questions already considered the need of improving both input databases and input practices, by explicitly recognizing (listing and explaining) and consistently handling issues associated with

- (a) treatment of non-detects,
- (b) presence of correlations in distributions of inputs that reflect exposure factors (as well as other, e.g., biological, parameters), and
- (c) limits/ranges of applicability of empirically derived ("fitted") regression equations used to parameterize inter-individual and intra-individual (e.g. temporal/behavioral) variability (again, both with respect to exposure and biological factors).

Development of population-relevant distributions of BLLs via Approach 3 (or via future refinements of Approach 3) can provide a useful tool for the support and assessment of health-relevant (or health-based, though, ideally that would require the explicit incorporation of mechanistic adverse outcome pathways linking exposure to biological effect through the BLLs) benchmarks for lead in drinking water. An extensively tested multimedia/multipathway framework for aggregate lead exposure modeling can provide valuable

support for comparative evaluation of alternative mitigation options that include the drinking water pathway.

"Supplementary" Reviewer Recommendations:

I. Though the document under review summarizes quite effectively a very large amount of information, there are occasions where a somewhat informal approach is used to make vague statements concerning important facts. Some examples are:

On p. 22: "...the low concentration of outdoor air lead being assumed in this analysis, air lead has a very small effect on overall blood lead values..."

On p. 28: "...the selection of input values in the case of soil and dust ingestion rate can have a significant impact on IEUBK model results."

On p. 29 "...estimated BLLs were much higher than national averages..."

The reader would definitely like to have a better/quantitative understanding of what is a "small effect", a "significant impact," a "much higher" estimate, etc. – a 10% difference can be negligible in one context but unacceptably large in another... It is therefore strongly recommended that statements such as the above are modified to include quantitative characterizations of effect/impact, etc.

II. In some cases there are statements that require resolution or correction, e.g.

On p. 29 it is stated the USEPA's "EFH does not specify whether the reported central tendency estimate is the arithmetic mean or the geometric mean." One would assume/hope that such an uncertainty can be clarified/resolved within the USEPA.

On Pages 58-59 it is stated that "[a] potential limitation of approach 3 is that IEUBK was only used as the basis for an analytical solution and was not used to allow its full capabilities of biokinetic modeling to estimate BLLs." However, the polynomial regression fit of IEUBK that is used in conjunction with SHEDS, in the formal mathematical sense is definitely not an "analytical solution" and should not be identified as such; it is an approximation that can be used the same way an analytical solution would be used.

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COMMENTS SUBMITTED BY

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External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

Acronyms

ALM = adult lead model
AM = arithmetic mean
ATSDR = Agency for Toxic Substances and Disease Registry
BLL = blood lead level
BLRV = blood lead reference value
BW = body weight
CDC = Centers for Disease Control
DW = drinking water
EBLL = elevated blood lead level
EFH = Exposure Factors Handbook
GM = geometric mean
GSD = geometric standard deviation
ICRP = International Commission of Radiological Protection
IEUBK = Integrate Exposure Uptake and Biokinetic model
MCA = Monte Carlo Analysis
NHANES = National Health and Nutrition Examination Survey
µg/dL = micrograms per deciliter

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA.

The selection of the three age groups make sense:

- The 0-7 year age group is a standard age range when running the IEUBK model and provides a benchmark for comparison with other shorter age group periods. A limitation of this averaging time is that the year-to-year variation in BLLs is sufficient to raise concerns that a health-based benchmark that corresponds to 7-year average exposures may not be protective of infants and toddlers, which represent sensitive developmental periods when potentially higher exposures and BLLs may occur.
- The 1-2 year age group is a good choice for a 1-year interval given the relative body-weight normalized water consumption rate is highest (and essentially equal to 2-3 year age group). Something like Table 1 (see next page) would be a helpful addition to the report; otherwise Exhibit 6 gives the impression that the 1-2 year age group is not the period of peak exposure since the water consumption rate is about 2.5-fold lower than that of the 0-1 year age group.
- The 0-6 month age group makes sense from the point of view of accounting for exposures to formula-fed infants. Evaluating exposures associated drinking water specific to formula-fed infants (Report Appendix A) is good, and is consistent with EPA's original recommendations on the use of the IEUBK model (see USEPA 1994a, Section 2.3.3.2). The major uncertainty is that NHANES data are not available from which to estimate baseline BLLs for this age group.

Table 1. Body weight (BW)-normalized water consumption rate by 1-year age groups.

Age Group[a]	GM Consumption Rate (L/day)[b]	Mean BW (kg)[c]	BW-normalized CR (L/day-kg)
0 to <1	0.410	7.2	0.0570
1 to <2	0.151	11.2	0.0134
2 to <3	0.176	13.3	0.0133
3 to <4	0.193	15.5	0.0124
4 to <5	0.197	18.0	0.0110
5 to <6	0.213	20.3	0.0105
6 to <7	0.228	22.2	0.0103

[a] The age range is presented inconsistently in the Report, and I recommend using the "<" symbol to clarify which age group is inclusive of the high end of the range. For example, Exhibit 5 is good (e.g., "0 to < 1 Years"), but Exhibit 6 has "0-1 Years" and "1-2 Years", which is ambiguous as to which group a person age 24 months is in.

[b] Based on Exhibit 6 of the report, which relies on NHANES 2005-2011.

[c] Based on Equation B5-f in the IEUBK Technical Support Document, also cited in the Report.

Some panel members recommended that EPA consider a scenario to reflect *in utero* exposure and risk to the fetus – which is of course the focus of the current EPA Adult Lead Model (ALM). I agree that it would be helpful to include a set of scenarios using the ALM model as a "check" on the range of water concentrations (benchmarks) calculated with the IEUBK model scenarios. I'd offer the following recommendations if EPA elects to expand the scope in this manner:

- Run the ALM model in "default input" mode and generate model runs that provide similar risk metrics as the Approaches 1, 2, and 3. That is, report on the delta in BLL at various points in the distribution after adding in a water consumption pathway, and report on the absolute blood leads and probabilities of exceedance of various reference levels.
- Run the ALM model in "updated input" mode, consistent with USEPA's current thoughts about the most up-to-date science on the age range relevant to women of child bearing age, water consumption rate, geometric mean and GSD BLLs.

I do not think additional life stages need to be modeled since the proposed age ranges effectively bracket the developmental periods of concern.

Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 µg/dL and 5 µg/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Drinking Water Only

I find it helpful to present results for a Drinking Water (DW) Only scenario, whereby all non-drinking water pathways are set to zero. However, EPA should reconsider the following statement, which is used to describe the rationale for this scenario (Report p. 42):

> "To explore the direct impact of drinking water alone, model runs were also conducted assuming no other sources of lead".

This implies that equal weight is given to the results based on the DW-only scenario, which I suspect will not be the case. It is highly unlikely that the final selection of a health-based benchmark would be based on this scenario, since it is expected that there will be a non-zero baseline BLL across age groups. The main utility of this scenario is to understand the incremental change in the various risk metrics once a baseline scenario is included. So I would recommend revising the rationale to something like:

> "To explore the impact of adding in a baseline (non-drinking water) contribution to BLL to each of the risk metrics, results are presented both for model runs excluding baseline (i.e., drinking water only) and including baseline."

It would be helpful to also run a baseline only scenario – so results would be available for baseline only, drinking water only, and finally – the combination of baseline and drinking water. As noted in my comments below (see Charge Question 3), I believe that baseline can be effectively represented by mining the summary statistics from the NHANES survey datasets, an approach that has already been used in published lead modeling research (Maddaloni et al. 2005).

Blood Lead Reference Values (BLRV) of 3.5 µg/L and 5 µg/L

The choices make sense in the context of a science-policy decision, given recent and ongoing discussions from CDC and its advisory panel, the Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP). However, in this Report, the rationale can be more clearly explained. As written, the clues are there – footnotes 15 and 16 on p. 41 give the 97.5th percentiles for the NHANES datasets for different survey years, and on p. 52, there is a reference to Zartarian et al. 2016, though the description of Approach 3 is very misleading:

> "Approach 3. Estimate the amount of lead in drinking water that would result in a population's predicted distribution of BLLs having a 95th or 97.5th percentile BLL of 3.5 or 5 µg/dL (Zartarian et al. 2016)"

Based just on this statement, the reader is lead to believe (incorrectly) that there is a distribution representative of baseline for which the 95th percentile is 3.5 µg/dL and the 97.5th percentile is 5.0 µg/dL. Later, in the summary of results, it is clear that both percentiles are evaluated for both target BLLs, however, the basis is not at all clear. Additional clues:

- Zartarian et al. (2016) state, "CDC is considering changing the reference value to 3.5 µg/dL (ATSDR 2016, p. 17)".

- ATSDR (2016, p. 17) states, "CDC is continuing to discuss the possibility of lowering the current BLRV from 5 to 3.5 µg/dL." And also, "The former ACCLPP voted to approve two recommendations to CDC in 2012. First, eliminate and replace the terminology of "blood lead level of concern" (i.e., >10 µg/dL) with a reference value based on the 97.5th percentile of the distribution of BLLs in children 1-5 years of age as measured by NHANES. Second, reevaluate the BLRV every four years. CDC concurred or concurred in principle with ACCLPP's recommendations."

From this information, it is clear that the basis for considering both a BLRV of 5.0 µg/dL and 3.5 µg/dL is that the former is the current CDC reference level based on the 97.5th percentile for 1-5 year olds from 2007-2011 NHANES, and the latter is the 97.5th percentile for 1-5 year olds from the more recent 2011-2014 NHANES, and will likely be adopted as a new reference value.

My specific recommendations to clarify the rationale are:

1. In Section 2.2 (Overview of Adverse Health Effects Associated with Lead Exposures), specifically in the second paragraph where public health agency perspectives are introduced, expand the text (or add a new paragraph) to talk about blood lead reference values (BLRVs) and CDC's current position. Introduce the term BLRV and use it throughout the report to promote consistency with ACCLPP's recommendations; do not use "target BLL" (as in the charge question above).

2. Introduce the 97.5th percentile summary statistics from NHANES here (you can repeat it again later in the footnotes 15, 16 too). Underscore the important point that an upper percentile of the distribution from NHANES does not denote a threshold effect level below which adverse effects are considered to be negligible; rather, it is a policy decision to establish a high-end BLL reference value that most of the population will not exceed.

3. Introduce the concept of how to interpret the percentile of a probability distribution of BLLs. It conveys the fraction of the population that is expected to have a BLL less than or equal to a specified BLL – this is the usual interpretation from the NHANES summary statistics. It also conveys a probability that an individual selected at random (from a group of similarly exposed individuals) will have a BLL less than or equal to a specified BLL. This is the context for which IEUBK model runs are typically interpreted. A short discussion along these lines will help set the stage later in the Report for how to interpret the model runs relative to the BLRVs.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

Each of the three modeling approaches uses a set of inputs to generate BLLs that reflect multi-media exposures. In the case of Approaches 1 and 2, only point estimates are used, and in Approach 3, a combination of point estimates and probability distributions are used. Importantly, the results are "ground-truthed" by comparing the predicted BLL distributions to BLL distributions reported from NHANES (e.g., Report p. 19). As explained in greater detail below (comments on Charge Question 3), an alternate approach

that uses distributions from NHANES more directly in the modeling may be preferred. This can greatly simplify the analysis while remaining grounded in data-driven evaluation of the key questions regarding the drinking water exposure scenario. If my recommendations are accepted, then most of the input variables are no longer needed, and one can focus specifically on the drinking water exposure variables. So my comments focus on these variables, but I also add thoughts on the maternal BLL and GSD (which would both still be needed), and the soil and dust ingestion rate, one of the more influential variables in the three approaches described in the report.

Drinking Water – Water Consumption Rate (L/day)

Exhibit 6 of the Report summarizes the age-group-specific input values used for average daily water consumption rate. I have the following comments:

- GSD calculation – all the values shown in Exhibit 6 need to be recalculated. As reported, they range from 0.0025 to 0.0035, which is not possible. Please double check your equations. Based on the other summary statistics that are reported, GSD likely ranges between 1.5 to 2.4 across age groups. Refer to Zartarian et al. (2017, Table S3) for GSD values that range from 2.5 to 3.5 – these seem high if in fact the other summary statistics in the table are correct and the distribution is approximately lognormal.

- The GM values (bolded in Exhibit 6) are used/proposed mainly to conform with the SHEDS model inputs, but EPA expects that central tendency inputs to the IEUBK reflect the arithmetic mean (AM) (USPEA 1994a). While I agree that updating the standard default values in IEUBK makes sense because the current defaults are based on much older survey data, the difference between the AM and GM is considerable and should, at a minimum, be highlighted in a sensitivity analysis. See Table 2 below for side-by-side statistics including the current standard defaults in IEUBK (which rely on analyses performed on survey data from the late 1970s), the Report Exhibit 6 (based on NHANES 2005-2011), and EPA's 2011 Exposure Factors Handbook (EFH) recommendations (based on both USDA's dataset from 1994-96 and 1998, and NHANES 2003-2006).

  Table 2. Summary statistics for consumption rates (L/day) of tap water (all uses).

Age Group	IEUBK Defaults[a] Mean	Exhibit 6[b] Mean	Exhibit 6 GM	EPA 2011[c] Mean
0 to < 6 months	0.20	0.662	0.526	0.287[d]
0 to < 1 years	0.20	0.581	0.410	0.324[d]
1 to < 2 years	0.50	0.247	0.151	0.271
2 to < 3 years	0.52	0.300	0.176	0.317
3 to < 4 years	0.53	0.316	0.193	0.327[e]
4 to < 5 years	0.55	0.320	0.197	
5 to < 6 years	0.58	0.364	0.213	
6 to < 7 years	0.59	0.377	0.228	---

[a] IEUBK defaults are based on USEPA EFH as of 1994, which largely relies on national survey data collected by USDA from the U.S. population in the late 1970's, as summarized by the EPA 1989 EFH.

[b] Exhibit 6 relies on NHANES 2005-2011 for all age groups.

[c] EPA's 2011 EFH relies on USDA's Continuing Survey of Food Intake of Individuals (CSFII) survey (1994-96 and 1998) for age groups < 3 years, and NHANES 2003-2006 for older age groups.

[d] EPA's 2011 EFH (Table 3-1) provides per capita means for ages 0 to < 1 month (0.184 L/day), 1 to < 3 months (0.227 L/day), 3 to < 6 months (0.362 L/day), and 6 to < 12 months (0.360 L/day). Values shown here are simple arithmetic means of 6-month and 12-month periods, after distributing monthly data based on the means reported.

[e] EPA's 2011 EFH (Table 3-1) provides per capita mean for 3 to < 6 years.

The following observations are clear from the side-by-side summary statistics:

- Given that each of the reported distributions of water consumption rates is positively skewed, the GM is a lower metric of central tendency than the AM. Therefore, the decision to rely on the GM instead of the AM as an input in IEUBK model runs will yield lower estimates of exposure from the drinking water pathway. Based on Exhibit 6, the GM would be expected to yield between 20% to 40% lower exposures.

- The Report (p. 24, footnote 9) explains that the inputs selected for this analysis are different from EPA EFH recommendations – higher for children younger than 1, and lower for children age 1 and older. This is only partially true. It would be helpful to add the percent difference in this explanation. For the children younger than 1, use of the more recent NHANES results supports estimates that approximately 57% higher for 0 to less than 6 months, and 44% higher for 0 to less than 1 year. For ages older than 1 to less than 5 years, the more recent NHANES results are lower than EFH by 2% to 10%. For ages 5 to 7 years, the more recent NHANES results are higher than EFH by approximately 10%. Therefore, for the 0-7 year age group, the more recent NHANES results are approximately the same (within 10%) of the inputs recommended in EFH.

I support the use of the more recent NHANES results as reported in Exhibit 6, however, the AM rather than GM values would be more appropriate for the scenarios used in the final derivation of a health-based benchmark.

Maternal BLL (µg/dL)

The Report (Section 5.10) provides a good justification for using a maternal BLL of 0.61 µg/dL in lieu of the current IEUBK default of 1.0 µg/dL.

GSD (unitless)

A default GSD of 1.6 is typically used (and recommended by EPA) when applying the IEUBK model (USEPA 1994a,b). The value was derived from several epidemiological studies and further tested by Hogen et al. (1998), who determined that observed and predicted probabilities of EBLL (defined at the time as > 10 µg/dL) matched to within 4%.

In these applications, it is important to recall that the GSD is the amount of variability in BLLs among children exposed to similar concentrations of environmental lead (USEPA 1994a; White et al. 1998). This is actually noted in the Report on page 14. For this reason, it is sometimes referred to as the "individual level GSD". It is a lumping term intended to account for exposure variability (except for the concentration term), biological variability, and measurement error. Note that Zartarian et al. (2017, p. 10) state that the GSD of 1.6 does not account for exposure variability, which is not true – as stated above, it accounts for essentially all of the exposure variability (e.g., activity patterns, hand-to-mouth behavior, media ingestion rates, etc.) except for the variability in concentrations across different households.

In the Report (Section 5.11), the GSD of 1.6 is used for Approaches 1 and 2 for all age groups except infants. The analysis presented to support a lower GSD of 1.45 for infants 0 to 6 months is good and makes sense. Approach 3 does not explicitly use a GSD, but rather relies on Monte Carlo simulation to propagate variability from multiple sources of exposure. There are several challenges for the different method used in Approach 3:

1. Variability in environmental concentrations is explicitly used, in contrast to the typical applications of IEUBK for which the goal is to represent variability in BLLs among children exposed to similar concentrations. This is done with the intent of representing variability in BLL on more of a national scale.

2. A child's exposure is simulated over time, using a series of short model time steps. With each time step, a new random value is selected from a set of probability distributions. If no correlation structure is applied to address intra-individual variability, then the shorter the time step, the greater the number of random values needed over a fixed exposure period (see comments on Charge Question 5 for more discussion). This has the effect of making each simulated child look more like the average child. Zartarian et al. (2017) settled on a 30-day averaging time. EPA explained that this means that results over a 30-day period are used to represent each of the age groups – so it is a decision about how to package the output (i.e., predicted blood lead distribution).

   EPA further explained that the time series is given by the diary information input to SHEDs, and that for each simulated child, approximately 4 to 5 random values are selected for each variable that is represented by a probability distribution. The process for implementing this micro-exposure event simulation in the Monte Carlo Analysis requires further explanation in the report because this was not at all clear to me prior to the public meetings.

   In the report, the implications of the time step needs to be explained in terms of the real effect that this has on the variance of the distribution. For example, if soil and dust ingestion rate is represented by a lognormal distribution with a specified arithmetic mean and standard deviation, then the process of selecting 4 or 5 random values (for each hypothetical child) has the effect of reducing the arithmetic standard deviation by the square root of n, or approximately a factor of 2 (i.e., sqrt(4) = 2; sqrt(5) = 2.2). This should be shown both graphically and in a summary table whereby the parameters of the "initial distribution" are given, and the parameters of the "effective distribution after random sampling" are also provided, assuming 4 to 5 random values are drawn. For example, consider the soil and dust ingestion rate for the 1-year old, which Zartarian et al. (2017, Table S3) indicates is

represented in the Monte Carlo simulation using an empirical distribution with the following parameters:

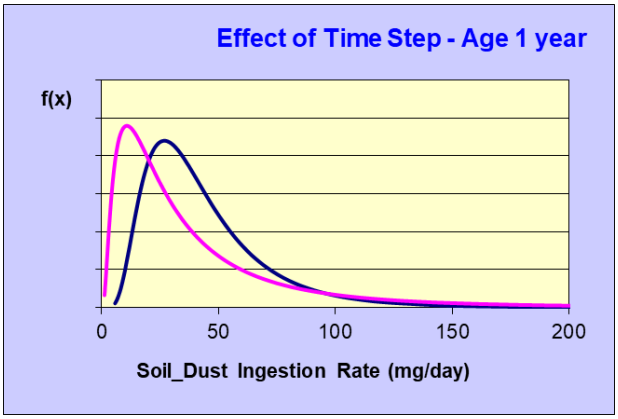
- Arithmetic mean = 43.9 mg/day
- Arithmetic standard deviation (SD) = 54.8 mg/day
- GSD = 2.8 (empirical PDF), or 2.6 if fit to a 2-parameter lognormal (mean, SD)

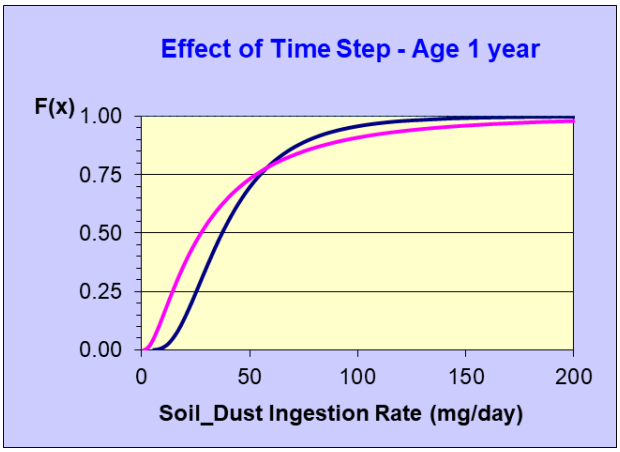
Assuming this distribution is sampled at random 4 times, the resulting distribution will have the following parameters (on average):

- Arithmetic mean = 43.9 mg/day
- SD = 27.4 mg/day
- GSD = 1.8 if fit to a 2-parameter lognormal (mean, SD)

That is, the effect of averaging the 4 or 5 random values is equivalent to sampling once from the distribution with the smaller SD. Given that the sensitivity analysis confirmed that the soil and dust ingestion rate parameter is one of the more influential variables on the predicted blood lead distribution, this reduction in variance that is attributable to the resampling will likewise have an effect on the GSD of the blood lead distribution generated by the Monte Carlo simulation.

Below is an example graphic that shows the original distribution (in blue) fit to a lognormal PDF and the distribution after resampling with n=4 random samples (in pink). The top graphic is the PDF view and the bottom graphic is the equivalent CDF view.





EPA also indicated truncation limits were imposed on the empirical distributions based on the survey results as entered into SHEDs. These truncation limits should be noted in a summary table in the report, along with the other summary statistics.

The main point is that different time steps (or numbers of random draws from the distribution) will yield different results, and serial (repeat) measurements of the same study population are typically not available to resolve this source of uncertainty. So the choice of time step, although derived from diary information, is still an extrapolation uncertainty because we are using short term survey data to represent long-term average behavior. This uncertainty has a direct effect on the uncertainty in the GSD of the simulated blood lead distribution. The effect of resampling should be conveyed for all of the variables that are represented by PDFs in the Monte Carlo simulations.

3. Approach 3 does not capture biological variability, so an adjustment procedure is applied, guided by a comparison to the GSD from NHANES BLLs.

Clearly Approach 3 is more complicated than approaches that rely on a user-defined GSD, requiring many decisions as far as distributions specified for input variables, model correlation structure and time steps, and adjustment factors to specify variance in BLLs. At the end of the day, given the specific charge question (developing a health-based benchmark for lead in water), the GSD of 1.6 seems to be better positioned to represent the aggregate sources of variability. Uncertainty can be represented by showing results for a range of GSD's that bracket 1.6 and perhaps low and high ends based on EPA's experience in lead risk assessments at specific communities. See comments on Charge Question 3 for additional discussion on the strengths and limitations of the proposed approaches.

Soil and Dust Ingestion Rate (mg/day)

The contribution to BLL from non-drinking pathways need not be explicitly modeled, as discussed in my comments to Charge Question 3 below. However, if these pathways are modeled, the following feedback is provided on the inputs that are proposed (Report Section 5.8).

Similar to the water consumption rate variable, the input values for soil and dust ingestion rate are guided by the values used in SHEDS (in order for Approaches 1, 2, and 3 to be comparable), rather than by a true recommended set of age-specific inputs. In addition, similar to the water consumption rate variable, the GM soil and dust ingestion rate is used in favor of the AM – EPA indicates in the Report (p. 28) that this is justified because use of the AM yields a predicted BLL that is much higher than national averages. So again, NHANES data are used to evaluate the plausibility of the model BLL predictions and thereby ground-truth the choices for inputs. It is unclear why/how a difference between NHANEs and BLLs can be attributed to a single exposure variable.

The Report includes references to Özkaynak et al. (2011) and von Lindern et al. (2016) and indicates that the different methods used by the separate investigation teams support similar values for older ages. Furthermore, the Report states that Özkaynak et al. is preferred because it provides a distribution, as opposed to a point estimate, for each age group considered. I question this logic since von Lindern et al. certainly supports probability distributions for each of the age groups as well (see von Lindern et al. 2016, Supplement Table S-1).

Özkaynak et al. (2011) uses an activity pattern modeling methodology to estimate soil and dust ingestion rates. EPA reviewed this study in the 2011 EFH (Section 5.3.3.5) and identified a primary limitation as lack of data to support inputs for some of the variables used in the estimation including:

- activity patterns of children in younger age groups, including children with high hand-to-mouth, object-to-mouth, and pica behaviors;
- information on skin adherence; and
- information on dust loadings on indoor objects and floors.

In addition, EPA 2001 EFH (p. 5-16) cites Özkaynak et al. (2011) results for ages 3 to < 6 years, but not other age groups of interest due to lack of data.

von Lindern et al. (2016) used a comparison of community-specific measured BLLs to predicted BLLs based on IEUBK model runs with site-specific exposure factors. More than 3,000 children participated in the study. A major benefit of this approach is that it relies on BLL, which is a time-integrated exposure metric, so there is no uncertainty associated with extrapolating from short-term survey results to long-term average behaviors. The main limitation of the analysis of the Bunker Hill community data by von Lindern et al. (2016) is the potential low bias introduced due to public awareness and community interventions to reduce exposure to lead. It is acknowledged that the awareness of lead exposure may have changed parental supervision of children, thereby reducing soil and dust ingestion. I suspect that the normal hand-to-mouth behavior of young children would not have been altered, but perhaps the parental influence on outdoor play areas and housekeeping to reduce indoor dust exposure could have introduced a low bias for some period of time. Given that a site-specific estimate of bioavailability was accounted for, the uncertainties associated with specification of other exposure factors in the model are minor in my opinion.

The bottom line is that, between these two studies, I believe the von Lindern et al. (2016) estimates of childhood soil and dust ingestion rate would serve as a more supportable source. Their use of the IEUBK model to adjust soil and dust ingestion rate in order to optimize the fit to the measured BLLs is scientifically sound, reproducible, and builds from a methodology that has a long track record of use in human health risk assessment.

Note that since the public meeting, another relevant article has been published, which uses the best tracer methodology (fecal tracer study) to estimate soil and dust ingestion rates for 177 children ages 2.5 to 12 years old living in three provinces in China (Lin et al. 2017). EPA may wish to consider this study as well in its analysis of the available literature.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular

percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

In this report, EPA uses the term "probabilistic" in a manner that is likely to be confusing to many lead risk assessment practitioners who have experience using IEUBK and ALM. For many years, EPA has previously characterized the IEUBK and ALM models as probabilistic models because the output is a probability distribution of predicted BLLs for various age groups. With IEUBK and ALM, variability is not propagated throughout the model equations using a technique such as Monte Carlo analysis (MCA). However, risk metrics are still expressed in terms of the probability of exceedance of BLRVs.

I also believe it may be confusing to categorize Approaches A and B as "individual-based", whereas Approach 3 is "population-based". Certainly the IEUBK model, run in a standard mode with recommended default inputs, has a long track record of assisting with risk management decisions directed at protecting populations and, in fact, is specifically not intended to be used to assess risk to an individual. I think this Charge Question is trying to highlight how Approach 3 is different because it explicitly models the multiple exposure pathways that are potentially contributing to exposure and BLLs for children throughout the U.S. Furthermore, variability in lead concentrations in various exposure media likely contribute to the distributions of BLLs observed in NHANES, so it makes sense to try to capture that source of variability also. But there's a simpler way to achieve this objective by using the IEUBK model coupled with a more direct use of the NHANES dataset – we'll call that "Approach 2.5", as my colleagues on the peer review panel suggested, and it is discussed below.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

In terms of risk metrics, EPA may want to consider a hybrid of Approach 1 and 3, whereby a health-based benchmark achieves two objectives: 1) limit the delta (change in BLL at some upper percentile of the distribution); and 2) limit the percentile value so that the probability of exceeding a BLRV is constrained to a small value. The latter is a more familiar risk metric for IEUBK model users – many are familiar with the former "P10" statistic, whereby the goal was to identify a media concentration (usually lead in soil) that limits the probability of BLL greater than 10 µg/dL to 5 percent. Likewise, the former "delta method" is a familiar risk metric in prominent national programs involving risk management of lead, including the National Ambient Air Quality Criteria for lead and the Lead Renovation, Repair, and Painting Rules. The delta method is also used in applications of California's Leadspread model (California EPA 2016). Strengths of both the delta BLL and the upper percentile (absolute) BLL is that they can be related directly to epidemiologic studies and CDC recommendations regarding BLRVs.

Approach 2 relies on a delta in the GM BLL. This approach can be evaluated without needing to impose a GSD assumption (as in Approach 1), or run a series of Monte Carlo simulations (as in Approach 3). So while it is relatively simple to implement and is not sensitive to uncertainty in methods used to quantify variance, it is unclear what the (health) basis is for a delta GM of 0.5 µg/dL or 1.0 µg/dL.

b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

The IEUBK model is an appropriate tool to evaluate a range of drinking water exposure scenarios. A major strength of IEUBK is that the model is easy to use, relatively simple to summarize, and model runs are readily reproduced. It can evaluate each of the risk metrics specified in the Report, including the Approach 3 metric involving exceedance probabilities of BLRVs.

The IEUBK model limits the average time for input variables to one-year increments. Therefore, it is more challenging to evaluate scenarios that involve short-term exposures (i.e., less than 1 year, but at least 3 months). However, as discussed below (comments on Charge Question 5), EPA's guidance on intermittent exposures as well as several published examples in the literature illustrate how this can be done.

"Approach 2.5"

Another strength of the IEUBK model is that it can be used to specify baseline conditions without having to model all exposure pathways. In a sense, it can be run in a "paired down" mode whereby all of the non-drinking water pathways are shut off, and replaced by the "Alternate Exposure" menu. This menu accommodates age-specific inputs of average daily intake, which can easily be converted to uptake by specifying an Absorption Fraction of 100%. An example of this is given below for the 1-2 year age group, using the input values specified in the Report to facilitate comparisons. The concept of building in additional pathway after having established baseline conditions (BLLs) has been used previously by EPA and published by Maddaloni et al. (2005).

Steps for Approach 2.5

1. Establish baseline using "Alternate Lead Intake" menu and zeroing out all other pathways.
2. Set maternal PbB to 0.61 µg/dL, per Section 5.10 (based on NHANES 2011-12 and 2013-14, pooled to create a 4-yr dataset for women ages 28-45 years, N=2,003).
3. Change the intake rate (µg/day) for 1-year age groups until the GM PbB for the age group of interest matches NHANES. For simplicity, set AF = 100% for alternate pathway.
4. Run IEUBK and select the option to display results as text (rather than graphics). Note what the corresponding uptake rate is for each age group (also in units of µg/day); even though AF=100%, uptake is slightly lower than intake due to nonlinearities in the uptake module.
5. Run IEUBK and select the option to display graphics. Only this display of results will show GM to 3 significant figures.
6. Match the GM PbB to 3 significant figures for NHANES age groups (add an extra zero to Table 1 of Zartarian et al. 2017):

Age Group	N	GM BLL (µg/dL)	
1 to < 2 yrs	475	1.16	>> add extra zero when matching with IEUBK: 1.160
2 to < 6 yrs	1,892	1.03	>> add extra zero when matching with IEUBK: 1.030

7. Assign baseline for each of 3 age group scenarios, noted below.

Age Group	GM BLL (µg/dL)	Notes
0 to 0.5 years (0 to 6 months)	1.160	Since NHANES does not report BLLs for < 1 year, this is an assumption.
1 to 2 years (24 to 48 months)	1.160	GM BLL for age group, matches the same age group noted above
0 to 7 years (0 to 84 months)	1.030	GM BLL for age group, assumed to be well estimated by 2 to < 6 yrs given above

8. Now add in a Water Ingestion scenario, using prescribed water ingestion rates from Report Exhibit 6, plus extra scenario for 0-6 month formula-fed population (Appendix A).

Age Group	N	GM (L/day)	
0-6 months	1,246	0.526	>> from Exhibit 6, based on NHANES 2005-2011. Use this for 0-1 year age group as input to IEUBK
0-6 months	346	0.640	>> based on USDA CSFII 1994-96 and 1998, as analyzed by Khan et al. (2013, Table 2b). Use this for 0-1 year age group as input to IEUBK

0-1 years	2,618	0.410	>> from Exhibit 6, based on NHANES 2005-2011 (for all remaining age groups). Use this for both 1-2 year and 0-7 year scenarios.
1-2 years	1,792	0.151	
2-3 years	1,848	0.176	
3-4 years	1,272	0.193	
4-5 years	1,358	0.197	
5-6 years	1,196	0.213	
6-7 years	1,306	0.228	

Table 3 below gives the results following these steps. Figure 1 is based on the information presented in the table. Note that the relationship between concentration in water and GM BLL is linear. The intercept (when concentration in water is zero) corresponds with the GM BLL reported for NHANES 2005-2011.

It is clear that similar graphics could be generated for other age groups relatively easily by running perhaps 3 to 5 different concentration in water to derive the linear relationship.

Once the GM BLL is estimated,

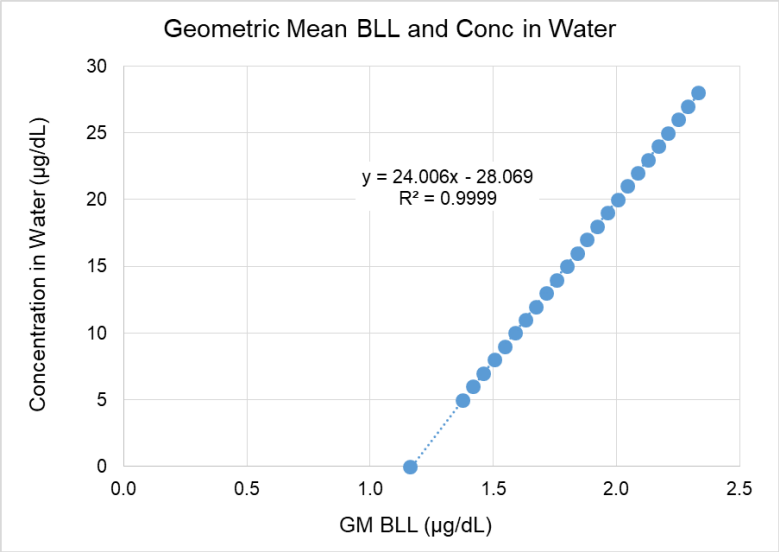


Figure 1. Example of relationship between GM BLL and lead concentration in water for ages 1-2 years.

Table 3. Example of "Approach 4" used to combine alternate (to reproduce NHANES BLLs) and drinking water exposure pathway.

Water	Uptake (µg/day)			GM BLL	P(BLL>x)	
µg/L	Water	Alternate	Total	µg/dL	3.5 µg/dL	5.0 µg/dL
0	0.000	2.599	2.599	1.160	0.938	0.094
5	0.368	2.591	2.958	1.375	2.341	0.301
6	0.441	2.589	3.030	1.418	2.725	0.366
7	0.514	2.587	3.102	1.460	3.146	0.441
8	0.588	2.586	3.173	1.503	3.603	0.527
9	0.661	2.584	3.245	1.545	4.097	0.624
10	0.734	2.582	3.316	1.587	4.627	0.732
11	0.806	2.581	3.387	1.630	5.193	0.853
12	0.879	2.579	3.458	1.672	5.795	0.987
13	0.952	2.578	3.529	1.714	6.432	1.135
14	1.024	2.576	3.600	1.755	7.103	1.297
15	1.097	2.574	3.671	1.797	7.807	1.474
16	1.169	2.573	3.742	1.839	8.543	1.665
17	1.242	2.571	3.813	1.880	9.309	1.872
18	1.314	2.570	3.883	1.922	10.105	2.095
19	1.386	2.568	3.954	1.963	10.928	2.334
20	1.458	2.566	4.024	2.004	11.778	2.588
21	1.530	2.565	4.095	2.045	12.652	2.859
22	1.602	2.563	4.165	2.086	13.550	3.147
23	1.674	2.562	4.235	2.127	14.469	3.450
24	1.745	2.560	4.305	2.168	15.408	3.771

25	1.817	2.559	4.375	2.209	16.366	4.107
26	1.888	2.557	4.445	2.249	17.341	4.460
27	1.960	2.555	4.515	2.290	18.331	4.829
28	2.031	2.554	4.585	2.330	19.335	5.214

Now each of the risk metrics can be solved for the concentration in water (Conc W).

Risk metric from Approach 1, using GSD = 1.6 and 1.9.

Approach 1

Baseline					Add 1%		Add 5%	
GM	GSD	>3.5	A = P(BLL > 3.5)	B = P(BLL > 5.0)	A + 0.01	B + 0.01	A + 0.05	B + 0.05
1.160	1.6	0.00940	0.00940	0.00094	0.019396	0.0109401	0.059396	0.05094

p	z(p)	BLL	GSD	GM	Conc W	
0.980604407	2.066	3.5	1.6	1.325	3.7	change of 1% exceedance of 3.5
0.940604407	1.560	3.5	1.6	1.681	12.3	change of 5% exceedance of 3.5
0.98905988	2.292	5.0	1.6	1.702	12.8	change of 1% exceedance of 5
0.94905988	1.636	5.0	1.6	2.318	27.6	change of 5% exceedance of 5

Sensitivity to GSD

Baseline					Add 1%		Add 5%	
GM	GSD	>3.5	A = P(BLL > 3.5)	B = P(BLL > 5.0)	A + 0.01	B + 0.01	A + 0.05	B + 0.05
1.160	1.9	0.04267	0.04267	0.01142	0.052666	0.0214156	0.092666	0.061416

p	z(p)	BLL	GSD	GM	Conc W	
0.947333922	1.620	3.5	1.9	1.238	1.6	change of 1% exceedance of 3.5
0.907333922	1.325	3.5	1.9	1.496	7.8	change of 5% exceedance of 3.5
0.978584381	2.025	5.0	1.9	1.363	4.6	change of 1% exceedance of 5
0.938584381	1.543	5.0	1.9	1.857	16.5	change of 5% exceedance of 5

Risk metric from Approach 2:

Approach 2

GM_baseline	+ Delta	GM	Conc W
1.160	0.5	1.660	11.8
1.160	1.0	2.160	23.8

Note: GSD is not needed for this approach

Risk metric from Approach 3, using GSD = 1.6 and 1.9:

Approach 3

p	z(p)	F(x)	GSD	GM	Conc W
0.975	1.960	3.5	1.6	1.393	5.4
0.95	1.645	3.5	1.6	1.616	10.7
0.975	1.960	5.00	1.6	1.990	19.7
0.95	1.645	5.00	1.6	2.308	27.3

p	z(p)	F(x)	GSD	GM	Conc W
0.975	1.960	3.5	1.9	0.995	-4.2
0.95	1.645	3.5	1.9	1.218	1.2
0.975	1.960	5.00	1.9	1.421	6.0
0.95	1.645	5.00	1.9	1.740	13.7

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

Clearly the SHEDS-IEUBK approach can be used to evaluate the risk metrics specified in both Approach 1 and 2. However, as shown above (Approach 2.5) and previously discussed, the SHEDS-IEUBK approach introduces several sources of uncertainty. These uncertainties are not necessary given the nature of the charge question.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

The SHEDS-IEUBK approach provides the most robust evaluation of relative contributions of variables and pathways to intake, uptake, and BLL. The output (BLL distribution) can be parsed into different percentile ranges to even more closely examine how the relative contributions may change as a function of, for example, quartile of predicted BLL. This is more robust than the one-at-a-time methods that are accommodated with IEUBK model runs.

However, I view this feature as "nice to have" but not necessary to answer the central charge question of what the concentration in water might need to be in order to achieve a health-based benchmark. Approach 2.5 introduced above capitalizes on the NHANES data as being representative of baseline conditions. To some extent, these conditions likely reflect a non-zero contribution of water already, so adding in another water pathway may amount to double-counting. This is unlikely to affect risk metrics based on "delta PbB", but it could be viewed as conservative (likely to overestimate risk) for risk metrics based on absolute BLLs like 3.5 and 5.0 µg/dL.

It is helpful to examine the sensitivity of the results to a range of plausible GSDs. This is true for any IEUBK modeling run, but particularly true here.

Note that the GSD of 1.6 is representative of the distribution of BLLs for children who are similarly exposed. Therefore, we can establish baseline, using different percentiles from NHANES (e.g., quartiles) as scenarios representing communities that may have a range of GM BLLs. As the contribution from baseline increases, the health-based benchmark will decrease for risk metrics that are based on the absolute BLL. But for risk metrics based on delta BLL, the health-based benchmark will be less sensitive to the choice of summary statistic used to represent baseline.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

I interpret this question about variability of drinking water concentrations at homes to mean that there is an inherent uncertainty in relating modeled estimates of exposure and risk to actual exposures that may occur in residential settings. With IEUBK, as with many exposure models used in risk assessment, the concentration term represents the long-term average concentration over a period of many months or years. It does not explicitly model short-term fluctuations or temporal patterns in concentration, but rather, assumes that the relevant metric is the long-term time-weighted and volume-weighted concentration. It is acknowledged that real-world exposures are intermittent (not continuous throughout the day) and may vary in both intensity and frequency.

I did not interpret "variability in drinking water concentrations" to imply that there are different exposure point concentrations at different households, which contributes to interindividual variability in exposure point concentrations. This interindividual variability does not need to be represented in the context of the use of the models to back-calculate a health-based benchmark for water. Thus, the essential question is framed as follows: *What concentration of lead in water is protective of a specified blood lead reference value?* The three approaches outlined in this report each examine variations of risk metrics based on the probability of exceeding a BLRV.

There are several approaches that can be considered to evaluate temporal variability, briefly discussed below. I do not believe that this issue represents a major source of uncertainty in the application of the models for the purposes of defining a health-based benchmark for lead in water. The models as proposed can be used to effectively represent a range of different potential long-term average concentrations. The guidance that accompanies the models can explain that, in practice, it is expected that there is short-term temporal variability in the exposure concentrations associated with drinking water that contains lead, which may result in short-term variations in BLLs.

a. Stochastic simulation – while we could use stochastic models to simulate long-term average exposures from a series of short-term exposure periods (e.g., micro-exposure event modeling – see Goodrum et al. 1996; Griffin et al. 1999; USEPA 2001), there is insufficient information on the kinetics of lead absorption, distribution, and elimination over such short time periods to believe that this added complexity reduces uncertainty. Furthermore, examining the fluctuations of BLLs over short time periods is not recommended. USEPA (2003, p.11) notes that the health effects (acute or chronic) of peak BLLs that occur after acute exposures are not well understood.

b. Model different locations – it's possible that individuals are exposed to lead via drinking water from different locations (e.g., primary residence, residence of a family member, day care, school, public buildings). USEPA (2003) provides guidance on use of the IEUBK model to simulate time-weighted exposures to lead in soil for scenarios where an individual engages in activities at a location at least one day per week for a period of at least three months. The same approach could be used to address lead in water. National surveys of activity patterns of the U.S. population could probably be used to simulate the plausible range of exposure scenarios among the U.S. population. In addition, we could

probably also simulate the plausible variations in the concentration term at these different locations.

However, from a public policy perspective, a risk assessment that supports a health-based benchmark that is protective of a scenario where an individual consumes all of their water from one source will also be protective of every combination of scenarios where they consume water from multiple sources (some of which may have lower concentrations of lead in drinking water). In short, it is conservative to assume a 100 percent fraction from the source with the highest concentration of lead. So, in my opinion, it is not necessary to add an activity pattern scenario that considers multiple locations of water consumption to the set of simulations in this report.

c. Model the acute exposure scenario – The model can be used to simulate seasonal variability such that we can consider the time period when the highest concentrations may be present in drinking water (or the combination of concentration and consumption rate yields the highest average daily intake rate). As noted above, the IEUBK model can be run to simulate exposures that may occur over a minimum of a three month period and guidance is available on this application.

Khoury and Diamond (2003) and Lorenzana et al. (2005) both present an analysis of short-term exposures to lead to illustrate that short periods of acute exposure can yield peak BLLs that are greater than peak BLLs predicted using IEUBK. To evaluate such acute scenarios, the ICRP model (developed by Leggett and coworkers) was used, which can simulate exposures to lead using a daily time step. USEPA has been testing the ICRP model for use as an "All Ages Lead Model" for lead, or AALM. A beta version of the model underwent external peer review in 2005-2006 (USEPA 2006) and, although not yet released to replace IEUBK and ALM, has been applied by various research groups as recently as the past couple of years (McLanahan et al. 2016; California EPA 2016). Lorenzana et al (2005) carefully examined the difference between adjusting the IEUBK model to account for short term, elevated exposures (by adjusting input variables) and simulating exposures with the ICRP model which uses a daily time step. Several observations were noted, which are relevant to the question raised in this charge question:

1. Defining inputs to represent a one-year averaging time (such as with the standard IEUBK application) may underestimate BLLs if there are sustained periods of elevated exposure, such as a seasonal pattern in lead uptake via water.

2. The magnitude of the underestimate depends, in part, on the relative contribution of the baseline exposures – in this case, baseline would be attributable to all non-drinking water exposure pathways. As the relative contribution of the baseline exposures to the total exposures increases, the potential for seasonal peaks becomes more important because the incremental contribution that can come from drinking water is reduced. This would be true for each of the risk metrics represented by the three approaches examined in the report.

3. One or more of the input values for exposure variables in the IEUBK model can be adjusted to represent the average over a shorter time period than one-year. Compared to a model like ICRP, which can simulate daily exposures, IEUBK run in this mode would be expected to yield higher

BLLs. This could be viewed as conservative (health protective), but without running side-by-side comparisons, it would be challenging to quantify the magnitude of the difference.

The bottom line is that temporal variability in concentrations and drinking water ingestion rates could be important. Seasonal variability in concentrations in water would not actually affect the health-based benchmark itself; this would be more of a risk management consideration – that is, how should tap water sampling be conducted in order to achieve compliance (e.g., during the season when peak levels are expected to be present). Seasonal variability in water ingestion rates can be handled by specifying an ingestion rate that corresponds with the peak seasonal ingestion.

The IEUBK model can continue to be used to explore this question, given that when it is run with appropriate inputs that reflect short-term (higher) averages, it will likely yield higher concentrations than ICRP. However, a rigorous sensitivity analysis would require an alternate modeling platform such as ICRP given the limitations in the model framework of IEUBK.

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COMMENTS SUBMITTED BY

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External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

GENERAL COMMENTS

This report represents a substantial effort that should be commended for its thoroughness, rigor and straight-forward, transparent presentation. The methods are fundamentally sound and adherence to appropriate scientific techniques and quality control is evident. If carried forward, with some adjustments, the methodology could be used to provide valuable insight to public health professionals and policy-makers in developing protective health criteria for children using US public water systems. However, EPA states this is only a statistical exercise, but nevertheless is developing a methodology with profound health implications. This makes it difficult to provide specific comments regarding the inputs to, and interpretations of, the output from these models without substantial caveats.

There have been some modifications made to the IEUBK analyses that, likely, render the current results spurious for public health or risk assessment. EPA does acknowledge that many of these modifications were made for comparative purposes and do not represent Agency policy; but it is difficult to ignore potential health implications. Moreover, whether the modifications are scientifically defensible, some are in direct conflict with EPA guidance, recommendations, and a history of regulatory decisions. In particular, it should be incumbent on the EPA to resolve how much water the Agency believes US children drink, consumption rates for incidental soil/dust ingestion, inhalation rates, time spent outdoors, etc. Each of the three main pathways (soil/dust, diet, water) have 50%-90% discrepancies in the consumption or intake rates between IEUBK recommendations, Exposure Factors Handbook guidance, and the SHEDS-derived inputs. Having each program select and support which databases and studies will be used in effecting national health protective actions is problematic. If the national databases conflict with EPA policy and practices, then the Agency should resolve the problems and direct the use of the most appropriate data. The Science Advisory Board has had a long and effective record in assisting the Agency in resolving such conflicts.

The conflict seems to center around the decision to input the exposure characterization developed for the SHEDS Approach 3 analyses into IEUBK Approaches 1 and 2, where these are both different in magnitude and inappropriate to the development of the IEUBK. The report indicates that this was done for comparative purposes, but it is confusing as to why one would want to compare one model's performance with the inappropriate use of another model; unless it serves to help and rectify the inappropriate data or variable constructs.

It seems that in initial comparisons of IEUBK and SHEDS blood lead predictions, EPA assumed over-predictions were due to out-of-date IEUBK default inputs that overestimate the consumption rates and determined to substitute alternatives derived from the SHEDs inputs. Although some updates to the IEUBK are in order and are under review in other committees, this overestimation of blood lead could also be due to simplistic point estimates of soil/dust concentrations that fail to capture the variance in US soil/dust exposures, and drive baseline blood lead levels. Applying the IEUBK across the national population, as accomplished in Approaches 1 and 2, encompasses large variation in several sources, co-factors, and exposure profiles that likely bring the application of the 1.6 gsd of the IEUBK into question when the SHEDS inputs are applied. It is also unclear if

the national databases used to develop the SHEDS inputs are reflective of the same populations encompassed in the NHANES surveys.

The EPA should also assess and discuss the extent to which the NHANES database captures the US most at-risk populations identified by the CDC and in notable incidents such as the Flint, Michigan crisis. More effective and reliable results might be obtained if Approaches 1 and 2 were developed for exposure stratifications of the national database and at-risk populations, using more appropriate consumption and ingestion rates and soil/dust lead partitions. These stratified results could then be evaluated within variously exposed communities to assess the effectiveness of health benchmark water concentrations. The national picture could be developed and compared to SHEDS Approach 3 by proportionately aggregating the stratified results.

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 µg/dL and 5 µg/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Life Stages: EPA has identified three age sub-groups with the impetus, presumably, to identify and assess potential outcome blood lead levels for the most vulnerable population sub-groups. Blood lead estimates will be developed through application of the IEUBK model for lead for each of the three age groups. Significant health risk will be evaluated by comparison of predicted blood lead levels to threshold health criteria (3.5 µg/dL and 5µg/dL). Several questions arise as to the appropriateness of these categories. It is generally recognized that younger children and fetuses are at greatest risk due to several intersecting factors, generally related to exposure, absorption, and health effects.

Exposure and Intake Considerations: Primary intake routes change markedly during the fetal to school-age development. Fetal exposure is maternal, largely reflecting the mother's blood lead level exacerbated by mother's nutritional status, diet, bone lead store, and habits (smoking, etc.) An infant's greatest exposure in the first 6 months is believed to be through breast milk, (thought to be reflective of the mother's blood lead status) or formula, the latter prepared by tap water being a central concern. Polluted air and dusts accumulating on surfaces (such as pacifiers) may add incidental increments. Additional exposure sources are introduced in the first year as children transition to solid foods (which may be contaminated), and begin to explore their environment through hand-to-mouth activities (incidentally consuming contaminated dusts in the immediate home environment). Substantial evidence suggests that incidental hand-to-mouth soil and dust intakes peak at 1-2 years until about age 4-5 years, and then decrease to typical adult levels around age 12 years. As toddlers, and then pre-school children, expand their immediate environment, additional soil/dust sources in the home, neighborhood and daycare environs become contributors; the greater community sources become important as children enter school and playtime activities. Drinking water consumption is largely formula-driven for the infant and then increases with age as children mature.

Absorption considerations: The bioavailability of lead intake also varies by each of these exposure routes (and within each route) due to both the physical and chemical characteristics of the intake media, and the

nutritional and behavioral predisposition of the child, which can also be age dependent. Generally, the most useful measure of overall absorption is the blood lead level which is often related directly to adverse outcomes in several organ systems.

Developing Organ System Considerations: Although numerous organ systems are adversely affected, the most particular concern is Central Nervous System (CNS) irreversible brain and nerve damage resulting in lifelong intelligence deficits and behavioral manifestations. These effects are most severe from conception through pre-school (5-6 years) as the CNS develops.

The challenge to EPA is to identify those age categories where exposure, absorption, and developmental factors combine to effect significant risk of unacceptable adverse outcomes. Because there are multiple exposure sources and co-factors with both individual and age-specific variation, more than one group may contain most vulnerable members. It is incumbent on the Agency that any protective measures adopted to mitigate these risks also be protective of all other age groups; and in this case with particular attention to the effects of drinking water exposures. The three age groups proposed are appropriate for the proposed analyses, provided the 0-7-year category is developed by year, and not in aggregate. It is likely that peak effects of drinking water lead exposure to infants occurs in the 0-6-month age period for formula–fed children, and it is advisable to evaluate this group separately. This is the age-group in which drinking water lead would be the primary (and perhaps only source of lead intake). However, it seems likely that drinking water (and associated lead) intake would increase as water replaces formula and total food intake increases as children grow and transition to solid food. This 1-2-year age dietary transition period coincides with peak soil/dust ingestion rates and is an appropriate age group to assess. Total lead intake and blood lead, however, may continue to increase as these children grow, access soil and dusts in the home and increase the dietary and drinking water lead increment. Peak blood lead levels may occur in the 3-4-year age range. This age band should also be evaluated separately, and not in aggregate with other age children in the 0-7-year analyses. Older children and adults would likely be protected by any action taken to mitigate 0-6 month, 1-2, 3-4 and 0-7-year risks, with exception of pregnant women as maternal absorption directly affects the fetus. As a result, potential fetal (or maternal) exposure should also be evaluated.

The 1-2, 3-4 and 1-7-year age groups have been extensively characterized and verified in numerous IEUBK model applications by the Agency, depending on the definition of age 0. Including children <1 year would be outside the traditional application of the IEUBK model. Less experience and verification have been accomplished with the 0-6-month old and none with fetal exposure, excepting some Adult Model applications that may be applicable. There is a need for more emphasis on fetal and maternal blood lead levels for nursing mothers with concurrent lead exposure. The uncertainties associated with placental transfer of lead, calcium demand on the mother as the fetal skeleton develops, maternal nutritional and behavioral considerations, and the mother's dietary (especially drinking water) lead intake need to be examined and appropriate margins of safety considered.

Modeling Scenarios: The Agency's proposed modelling strategy to address these combined exposure and absorption effects and organ exposures and vulnerabilities is somewhat different than the typical approach of identifying the most vulnerable population and then presuming mitigating exposures for that group protects all members of the population. There is confusion associated with EPA's short and long-term assertions that, on one hand, this is a statistical exercise to adapt the IEUBK to fit national databases and is

not health-related, versus developing a model to facilitate risk assessment and mitigation programs that will be used to develop quantitative health indices and regulatory action levels. It is difficult to provide meaningful comment on the appropriateness of any modeling exercise without knowing the purpose of the model or how it will be used.

The strategy to develop model scenarios that evaluate blood lead increments for drinking water only, and all pathways combined, suggests dual or multiple purposes. From a risk assessment perspective, the water-only scenario seems most applicable to 0-6-month formula-fed children as a most sensitive group, due to the high intake rate of water (actually *dose*, both absolute and relative to other sources). This age group is of particular concern as it may be the most vulnerable to water lead exposure, most susceptible to spikes in exposures, and least understood with respect to modeling blood lead or health effects. EPA should develop the discussion of these uncertainties, conduct appropriate quantitative and qualitative sensitivity analyses, and consider these in the context of approaches by WHO, and other international organizations and countries that have developed health-protective water criteria for infants.

It also seems essential for health and risk assessment that older children be evaluated with aggregate exposures, assessing risk relative to the likelihood of exceeding the threshold health criteria. This is because developmental vulnerability, higher co-exposures, and additional exposure co-factors combine to exacerbate intake and absorption in some children with age.

The use of IEUBK to assess water-only scenarios for older children suggests the Agency is developing a platform for either assigning relative liability to the various sources, or determining risk increments for children that have minimal exposures and blood lead levels. Having minimal or high exposures in the US today is most often dependent on sources and risk co-factors related to socio-economic advantage or disadvantage. As a result, these potential evaluations raise both risk communication and environmental justice issues, as the IEUBK has been used extensively to allocate responsibility for increased absorption among the sources of lead. The difficulties of making source allocation determinations in those regulatory and litigation schemes are well-known and reflect the shape of the dose-response and health effects curves at lower blood levels. In analyzing the nonlinear absorption and health effects predictions generated in a multi-media exposure scenario, relative contributions can be manipulated by the order in which the sources are introduced into the models.

Current consensus is that the first lead introduced at the lowest blood level is absorbed at a higher rate and does more organ damage per unit of absorption. Thus, fetal lead might be expected to result in the highest unit rate of irreversible health damage; and the difference in risk and manifestation of adverse effects between unexposed or advantaged (e.g., middle and upper income, white, post-1970 suburban) mothers and fetuses and the poor living in areas with sub-standard housing and deteriorating infrastructure may be marked. Relative risks to those with even low exposures (e.g., urban, low and middle income, mixed-age housing) may be significant when compared to more affluent communities. Maximum relative risk (and the highest rates of absorption and adverse health effects) due to water alone may well occur in formula-fed infants, as EPA alludes to in the discussion; and the differences in risk and outcome between exposed and minimally-exposed populations might be notable. The most severe adverse health effects, however, are likely associated with the highest blood lead levels due to all sources combined. In these cases, incremental exposures due to any source (i.e., drinking water) introduced to a child with an already high blood lead level

will significantly exacerbate overall risk, but at a lower (but nevertheless deleterious) absorption rate. These children are also likely to be among the more disadvantaged due to poverty, housing, and other socio-economic factors.

Although EPA does introduce drinking water lead both as the initial source (in the drinking water only scenario) and as an addition to other sources (incremental), it is troublesome that EPA's analysis implies markedly different source attributions than would be indicated with application of IEUBK default parameters (see Model Input discussion below). The results could be interpreted to imply that the most severe drinking water health effects could be expected at lower concentrations in affluent communities, while higher levels could be accommodated in poorer communities already experiencing excess absorption. Although EPA indicates that this is not a health-related analysis, but rather is a statistical exercise to fit observed blood lead distributions, it is difficult to imagine future uses of these models that will not be health-related. In the development of any health benchmark, the eventual risk communication challenges to water purveyors, public health, school and community advocates should be a paramount concern.

Target Blood Lead Levels and Upper Limits of the Blood Lead Distribution: EPA justifies the "non-health related" purpose of this exercise in the definition of Elevated Blood Lead Levels (EBLLs). For the purposes of this analysis, EBLLs were defined as at or above 3.5 µg/dL or 5 µg/dL, and emphasizes that these levels are not based on preventing adverse health outcomes, but rather on a statistical approach considering BLLs at the national level (i.e., the 97.5th percentile BLL based on 2011-2014 and 2007-2011, NHANES data for 1- to 5-year-old children, respectively). Despite the denial that this analysis is health-related, blood lead criteria, effectually, have always represented both a health effects threshold and an upper limit of the contemporaneous national blood lead distribution. This has evolved through a continuing cycle of recognizing adverse effects at contemporaneous levels, effecting policies to reduce overall blood lead levels, observing more deleterious effects at the lower blood lead levels, and initiating additional measures to further lower absorption levels. It was recognized long ago that this trend will continue toward zero blood lead, as there is no safe level of lead. EPA should indicate what health threshold levels the Agency believes are applicable at this time, and whether those differ significantly from the statistical upper limits of the populations evaluated. If these levels are not significantly different, then reviewers are hard-pressed not to consider health implications.

EPA's strategy of evaluating drinking water lead levels associated with both mean per unit blood lead increments and 0.5% and 1.0 % changes in the number of children expected to exceed the 3.5µg/dL and 5.0µg/dL blood lead criteria suggests an attempt to accommodate a constellation of potential uses of the results. The document under review alludes to a strategy of assessing the results against a target distribution of 95% and 97.5% of children below these blood lead levels. It is difficult to comment on the appropriateness of these criteria and percentiles without knowing why and how the comparisons will be applied. It is doubly difficult, and would require pages of qualifying statements, to comment on the appropriateness in the context of the IEUBK applications, model inputs, model type employed, and whether the percentage criteria are treated as the proportion of the population meeting that criteria, or the risk that an individual in that population will exceed that criteria. All of these selections must be made in concert with the intended uses of the model.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

As noted above, it is also difficult to provide meaningful comment on the appropriateness of the input variables without knowing the purpose of the model or how it will be used. The report notes that:

> "Due to the national scope of this exploratory lead modeling effort, and given the additional exposure modeling possibilities made available with the SHEDS tool, EPA modified several of the default inputs to the IEUBK model. The modified input values were developed from a number of national-scale data sources that were available to the Agency at the time this set of potential modeling methods were being developed. The selection and use of these input values are for illustrative purposes to allow for ease of comparison across model approaches. The purpose of this report is to obtain feedback on various lead modeling methods that can be used to characterize the relationship between lead in drinking water and children's BLLs. The input parameters used in this analysis do not represent high-end exposures."

With regard to the short-term purpose of successfully emulating the NHANES blood distribution by modifying the IEUBK input variable values, and using these same inputs in individual IEUBK Approaches 1 and 2, the analyses show consistency in results. It would be surprising if this were not the case, as decreasing the intakes will reduce the blood lead estimates. Interpretation of the data also shows that modeled impacts of drinking water lead varies according to whether water lead, or other sources, is first input to the model. This result is also not unexpected. This is likely indicative of competent model structure and development. Nevertheless, the modifications to the IEUBK input parameters substantially change the outcome predictions in comparison to recommended EPA default scenarios; and have marked effect on any health-based benchmark that might be derived from the results.

A simple comparison of the percent changes in key input values in contrast to the IEUBK default parameters shows the results are clearly biased toward effecting maximum water lead benchmark concentrations. The following Table from Exhibit 17 shows that the modifications to IEUBK inputs reduce the default soil and dust lead intake by 93%, diet by 88% and air lead by >90% allowing the water source to accommodate substantially more lead, and markedly increasing the "health benchmark level".

From Exhibit 17.

Variable	Input	IEUBK Default	Percent Reduction
Inhalation	3.82	5	24%
Soil/dust Ingestion	0.029	0.135	79%
Water Intake	0.193	0.53	64%

Air Pb	0.01	0.1	90%
Soil Pb	37	200	82%
Dust Pb	72	150	52%
Diet Pb	0.27	2.26	88%
Maternal Pb	0.61	1	39%
Soil/Dust Pb Intake	1.6	23.3	93%

EPA justifies these substantial modifications by noting that i) application of the default input variables predicts mean blood lead levels substantially greater than those observed in the NHANES surveys; ii) the default values are out of date, iii) the intent is to rely on national databases previously used in the SHEDs analyses, and iv) the use of geometric means to characterize typical exposures, also consistent with SHEDs.

Over-prediction by Default Values: It is not unusual for the EPA recommended default parameters to overestimate typical blood lead levels in numerous settings. EPA notes that most of the IEUBK default values were determined during the "Superfund Era" when blood lead levels were higher. In addition, several of the input default recommendations were conservative and were applied in the absence of site-specific data, such as soil and dust concentrations, which EPA encouraged be obtained. EPA has also developed the Exposure Factors Handbook to provide typical values for exposure co-factors to be used in risk assessment and mitigation, also in the absence of credible site-specific data.

Out of Date Values: It is common, in fact encouraged, in IEUBK analyses to substitute credible site-specific data for the default values. This is particularly the case for media concentration and absorption variables that usually vary by site and can be directly measured. It is less common to modify the consumption variables as this implies that the population's habits and practices are site specific. Although the default media concentration values may need updating to reflect current exposures, it is less likely that children's incidental ingestion and water consumption habits have changed. In this report, EPA has elected to substantially modify these consumption, or exposure rate variable values, based on a desire to remain consistent with the national databases used to derive probabilistic variables for the SHEDS analyses. These databases have been noted to provide estimates lower than those relied on in the Exposure Factors Handbook and IEUBK model guidance and EPA has cautioned against using these sources in the past. Other EPA work groups are currently engaged in scientific reviews to update both the IEUBK and Exposure Factors Handbook recommendations. EPA should endeavor to see that those efforts and the development of the SHEDS model ingestion and water consumption estimates be consistent with each other and the recommendations of those advisory board findings.

National Data Bases and Geometric Means: There are two main discrepancies among inputs in these analyses and typical IEUBK model applications: (i) the use of national databases that tend to underestimate exposure factors and exhibit large variances, and (ii) the use of geometric versus arithmetic means. Both are contrary to the development and evolution of the model and the published guidance. Simply substituting geometric means in the IEUBK inputs for these three key variables will inevitably reduce each source's contribution to the calculated mean blood lead estimate. In addition, the application of the 1.6 gsd in the

model to derive exceedance estimates is an empirical compromise based on practice and observations spanning years of applications. This calculation of percent to exceed threshold values anticipates neither the lower central tendency estimates calculated from the geometric mean inputs, or the huge variances inherent in the national databases. Simple substitution of these values into the IEUBK, as accomplished in Approaches 1 and 2 may facilitate comparison to the SHEDs output, but nevertheless will produce spurious results. EPA notes in the report:

> "The selection of the geometric means for use in the two IEUBK-based modeling approaches is due to the lognormal distributions of the input data. Utilizing geometric mean input values differs from the use of arithmetic mean input values which were used in the evaluation of the IEUBK model. The IEUBK model results using geometric mean inputs are specifically intended for the purpose of comparing the utility of the three modeling approaches presented in this report and may not be generally applicable to other analyses. The selection of the geometric mean for exposure rate inputs (water ingestion, soil and dust ingestion, and dietary intake) in this draft report should not be construed as a recommendation for their usage as an input parameter in the IEUBK model."

This explanation is somewhat confusing, as the remainder of the report is an exercise in fitting the IEUBK to national blood lead distributions by substantially modifying the input parameters. EPA attempts to justify these modifications by comparing the variable distributions to national databases. However, in past efforts other EPA entities have cautioned against relying on these databases in developing both the Exposure Factors Handbook and recommended IEUBK input values. The IEUBK model has been developed to accommodate average exposures. Substantially modifying the intake rate inputs implies that the population (in this case the NHANES database) practices substantially different consumption habits than the populations anticipated in the IEUBK guidance.

EPA identifies above the most troublesome rate inputs in the above quotation (water ingestion, soil and dust ingestion, and dietary intake). The water intake values used for older children is about 1/3rd of the IEUBK default recommendation. The large reduction seems to be related both to differences in consumption rates between the databases relied on, and on the use of the geometric rather than the arithmetic mean. EPA should discuss this selection in the context of the findings of Agency work groups and advisory committees currently engaged in scientific reviews to update both the IEUBK and Exposure Factors Handbook recommendations. EPA should endeavor to see that the Agency's characterization of the US population is consistent across programs, analyses, and development of health-protective measures, particularly as this is related to the drinking water standard. It seems EPA should be consistent across the Agency in its understanding of how much water US children consume.

As EPA indicated, it is important to note that the selection of input values for soil and dust ingestion rate can have a significant impact on IEUBK model results, and the nearly 80% reduction in the soil ingestion rate is probably the most significant modification. EPA elected to estimate the soil and dust ingestion rate distributions by age based on models by Ozkaynak et al. (2011). This study predicted mean and 95th percentile total ingestion of soil and dust values of 68 and 224 mg/day, respectively; and indicated a total soil and dust ingestion lognormal distribution with geometric mean of 35.7mg/day and gsd of 3.3. Although

it is unclear how the value was derived, EPA used a geometric mean of 26.6 mg/day in Approaches 1 and 2, stating:

> The geometric mean of 26.6 mg/day used in approaches 1 and 2 is less than the recommended EPA *Exposure Factors Handbook* (2011) "central tendency" values of 60 mg/day for individuals <1-year old and 100 mg/day for individuals between 1 and 21 years of age. A sensitivity analysis was conducted using the EFH central tendency value of 100 mg/day (by scaling the Ozkaynak et al. (2011) modeled distribution for the baseline runs). It was found in doing this that estimated BLLs were much higher than national averages, and therefore the input value of 100 mg/day was assumed to be too high for this analysis.

The latter assumption is particularly troublesome, and it is questionable as to whether this justifies applying input values resulting in 93% reduction in lead intake. It is also important to note that in SHEDS the much lower time outdoors value and the empirical relationship used to convert dust loading to dust concentration both further reduce the soil/dust intake rate. As noted above, the IEUBK default values often tend to overestimate observed blood lead levels. Both the Exposure Factors Handbook and IEUBK default values are consistently around the 100 mg/day for older children. More recent studies indicate typical ingestion rates may be closer to 60 mg/day. Both Ozkaynak et al. (2011) and this reviewer (von Lindern et al. (2016)), are cited in support of a 60-70 mg/day value. It is unclear how "scaling up" the modeled distribution was accomplished, but simply substituting 100 mg/day for the central tendency and employing the same gsd seems questionable. More important, however, is to remember that the lead uptake component in the IEUBK is the product of ingestion rate, soil and dust lead concentration, and bioavailability. It is also possible that the overestimation noted in the scale up analysis is due to the soil/dust lead concentrations or bioavailability used in the analyses. Both were input as point values, and much of the variation inherent in these variables may be subsumed in the large variation attributed to the ingestion rate. The relatively flat ingestion rate employed across all age groups is also troublesome. The use of the 1-year old rate for infants 0-6 months is likely inappropriate, especially considering that there is little difference among the ingestion rates used for all aged children, implying that formula-fed infants ingest as much soil and dust as 4-year-old children (Exhibit 9).

Effective IEUBK analyses require careful specification of the soil/dust input variable. Children are exposed to various sources in their daily activities. Recent studies show that soil/dust exposure comes from within the home, home yard, play areas, neighborhoods and across communities. Each of these sources can have unique concentrations and bioavailability, and can vary independently. Relative contributions of these sources must be partitioned and proportional concentrations and bioavailability developed for the single individual inputs provided to the IEUBK. The variation should be captured by providing unique estimates for each individual input in batch mode. It is not uncommon that substantial contributions come from beyond the home, and are characteristic of the neighborhood and community. Older, less affluent, or industrial communities may present higher neighborhood and community soil/dust exposures for these children. The values are derived from the healthy homes surveys in this report, are limited in scope, and represent a broad spectrum of housing types and communities across the country with only two-point values.

More effort should be applied in sensitivity analyses utilizing other ingestion rate inputs; e.g., von Lindern et al. (2016) has age-specific arithmetic means similar to Ozkaynak et al. (2011), but with larger geometric

mean and much lower gsds. EPA did use the von Lindern et al. (2016) distribution for 2-year children in additional sensitivity analyses in the Supplemental Materials addendum to the recent EHP publication provided during the review period (EHP1605R2). These analyses could be enhanced by applying the technique to other age groups, as the 2-year old ingestion estimates in von Lindern et al. (2016) are the most uncertain and likely to over-predict blood lead levels. More sophisticated construction of the soil/dust exposure inputs should be developed, including consideration of community soils, and alternate dust lead concentration estimation. It is advisable to avoid drawing conclusions regarding the source of overestimation of observed blood lead levels in non-linear multiplicative models based on manipulating a single variable. A more appropriate sensitivity analyses would to be use Exhibit 9 from the report for von Lindern et al. (2016) and apply it with a more sophisticated soil/dust lead concentration distribution.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

AS EPA notes, Approaches 1 and 2 apply the same model to project outcome blood lead levels. Both approaches develop the same baseline blood lead distribution resulting from sources other than water. Approaches 1 and 2 differ only in how the results are presented. Both methods determine a baseline blood lead level from other sources and then add water lead increments to the model to effect blood increases. As noted above, manipulations made to the IEUBK input likely yield spurious baseline results for the purpose of health risk assessment; but with appropriate inputs the methodology is sound. Approach 1 focuses on the tail of the response generated from the distributional module and identifies water lead concentration that increase the probabilities of exceeding the EBLLs by 1% and 5%. The result can be interpreted as the incremental probability that an individual child will exceed the threshold level due to the water lead source, or the number (or percentage) of children whose blood lead levels will increase above the threshold. Because these predictions occur in the tail of the distribution, there is less certainty than the prediction of changes in the mean in Approach 2. The utility of the result is that EPA could develop a "benchmark policy" defining unacceptable risk in terms of the probability of exceeding a health threshold. The public health official, parent, or school superintendent who receives this notice would be hard-pressed to interpret this in practical terms, other than to say EPA thinks it is too high. In reality, the 1% or 5% increase due to water lead implies these children move from slightly below the threshold to slightly above the threshold, not from safe to unsafe. An important question for EPA is how the threshold is defined.

Approach 1 has the additional problem in the current report that input of geometric mean ingestion rate estimates for soil and dust based on a logarithmic distribution with a gsd>3, diminishes the validity of the 1.6

gsd used to calculate percentile values in the distribution module of the IEUBK (See Response to Question 3c). As a result, the water lead levels estimated in the current report were derived from the tail of the distribution and are likely doubly unreliable for health risk assessment purposes.

In Approach 2, candidate benchmark water concentrations are derived from baseline geometric mean BLLs, by determining the water lead increment that would increase the mean by 0.5 µg/dL or 1.0 µg/dL. This methodology is also sound, but with the caveat that the means were calculated inappropriately, as noted above. This calculation has more certainty as it is performed at the central tendency of the distribution. The results can be interpreted as the increase in blood lead level the typical child will experience from drinking this water, and there is a particular loss of IQ that can be related to the blood lead increment, again for the typical child. However, the child with the mean, or most likely or typical, response is not the most at-risk. The larger concern is with the children in the upper tail of the distribution who will have a greater baseline value and incremental response. That response and total lead level, however, can be calculated from the mean at any percentile of the population; and can be related to potential IQ loss, as well. For example, the benchmark notice could be transmitted with the interpretation that the typical child would experience a 1.0ug/dL increase, with some children as much as 2.0ug/dL. This interpretation seems easier to comprehend and more practical for the parents, school officials and water systems authorities that receive the benchmark notice (e.g., your child is likely to lose 1 or 2 IQ points from drinking this water).

However, in the interests of openness and transparency, there remains the problem that these effects are incremental to the baseline for both blood lead and IQ. The baseline also has associated risks of adverse health effect risks. In most affluent, rural and newer suburban communities the baseline blood lead levels are low; but the bulk of the overall effects are associated with mainly the water lead increment. In already exposed communities, the water lead should be interpreted as increasing ongoing adverse effects and further depressing IQ.

As an alternative Approach to better assess and convey both these risks, the models could be run for a series of baseline blood lead levels. The results of Approaches 1 and 2 could be combined in age-group specific matrices with columns indicating incremental water lead concentrations and rows indicating baseline blood lead means. The matrix cells for Approach 1 would contain %-tiles to exceed EBLLs. These %-tiles could be interpreted to represent the probability a child from that background environment would exceed the EBLL level. EPA could then stratify the national exposure profile and develop aggregate background BLL representing exposure indices for US communities (e.g., post-1970 suburban communities, rural, mid-sized cities, inner city low quality housing, etc.). The potential effectiveness of water concentration levels could then be evaluated in terms of effectiveness in moving children below threshold values and exposure profiles (or communities) where the target EBLLs cannot be achieved.

Similar matrices could be developed for Approach 2 indicating predicted blood lead increments at select distribution %-tiles (e.g., 50, 95, 97.5). A zero-background blood level could be included to evaluate the impact of water alone. These analyses pre-suppose that appropriate inputs are made to the IEUBK. This would include modifying the ingestion rate values and developing more representative soil and dust concentration partitions for the stratified exposure scenarios. EPA also asserts that population wide-estimates of relative source contributions available from the SHEDS output cannot be accomplished with the IEUBK. The IEUBK does provide relative contributions for a population of similarly exposed children.

Estimates of relative contributions for the national population could be obtained by aggregating IEUBK runs stratified for the US population. This would be an amplification of the IEUBK application for children in homes with lead paint in Appendix B. That is, a series of defined exposure stratification scenarios that encompass the US population that could be aggregated proportional to population. Comparisons to SHEDS or NHANES could then be made to aggregations of the stratified Approach 1 results. Or, the SHEDS output could be used to inform the exposure stratification scenarios to be developed as case histories by the IEUBK.

In Approach 3, EPA developed a national baseline distribution of daily lead exposure in µg/day from probabilistic background (all sources other than water) lead concentrations and children's activity patterns. Water lead was then added to determine the concentrations that could keep blood lead levels at specified percentiles of the simulated U.S. childhood population below specified "targets." Approach 3 results are useful in assessing the national implications of drinking water lead levels, in relation to the overall lead exposure distribution and current baseline blood lead levels. These results could be used to evaluate the number of children nationwide that might be affected from implementation of various benchmark levels. However, it does not help in evaluating the effectiveness of the "target" level, other than identifying the percentage of children nationwide that cannot be brought under the threshold, even at zero water lead. (See the historical discussion of the "target level in Response to Question 3c).

EPA notes the ability to evaluate the contribution of all exposure pathways to BLL across the distribution of BLLs and asserts that population-based approaches allow a better characterization of variability in physiology and exposure than those based on a modeled individual, which EPA suggests is not possible with the IEUBK. These assertions require some qualification. Approach 3 estimates the contribution to total absorption by pathway for the aggregate US population (as represented by NHANES); but that applies to children in total across the population and national exposure profile. Although this is of considerable use in assessing the national implications of implementing health protective policies, these results can only be interpreted as "somewhere in this country this number of children are suffering lead poisoning and reducing their drinking water exposure will provide relief to some number of them." In addition, EPA notes "population-based approaches are consistent with previous EPA methods for assessing lead exposures." Of course, in order to do so, EPA will have to determine what blood lead level constitutes lead poisoning (or accept CDC's definition), what percentage of the population over that threshold is excessive, and how to mitigate risk for those children (See Response to Question 3c).

b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

A primary strength of the IEUBK model is that it does predict blood lead and probability increases associated with exposure increments to baseline exposure scenarios reflecting other sources in children's environments; and it does indicate the relative route-specific intakes, uptakes, and contribution to blood lead. As a result, risk management decisions can be based on both incremental and total risks. It is possible to convey to parents, school officials and public health practitioners both the incremental effects of contaminated water and the potential for overall lead health damage in their communities, as opposed to the entire country. That is, provided the community baseline is known. The IEUBK has the distinct advantage that it can be applied to particular baseline situations and provide site-specific (or scenario-specific) results, as demonstrated in Appendix B. The output from these site-specific or representative community scenarios can be used to

determine the "target" percentile in those communities where media-specific regulation becomes ineffective in keeping children below health criteria.

The principal weakness in IEUBK applications is predicting the blood lead response to short-term spikes in exposure, or a series of spikes, as the IEUBK kinetics assume steady-state exposures over a lifetime. However, relatively little is known as to the actual effects of these exposures, so this represents a gap in knowledge regarding lead poisoning response, as well as the inability to model the same mathematically, as is the case with most environmental contaminants. The report would benefit from a more extensive description of the variability of lead concentrations in the more at-risk water systems, particularly with regard to the extreme short-term spikes in concentrations related to physical, chemical, or water quality changes. The IEUBK operates in the chronic to sub-chronic exposure and disease spectra; whereas the exposures of concern in many of these events might be considered sub-acute and other assessment, modeling, or response strategies might be considered.

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

Overall, the use of the SHEDS model to estimate increments in geometric means or percentage to exceed threshold concentrations in the tail of the distributions brings up several questions with respect to its utility in developing and employing a benchmark health standard. A most fundamental consideration is evidenced by the many comments elicited by the SHEDS application. Most of the effort in Approach 3 is directed at trying to develop a national distribution of lead intake using scores of variables and distributions. This expansive undertaking is, doubtless, a valuable research exercise that should be pursued and will likely become an important tool in assessment of the national health picture with respect to numerous contaminants and exposure pathways. In this application, however, most of the attention has been diverted to critique of the input variables and notable weaknesses related to variable constructs, correlations, truncation, appropriateness of catch-all variance assumptions etc., and not on the health implications implied by the outcome blood lead levels. The use of a simple blood lead level platform (baseline blood lead levels related to US communities) might be more utilitarian in conveying the potential implications of contaminated water in a particular US community.

With respect to estimating changes in geometric mean levels, the health significance of the geometric mean blood lead level of the exposed population is difficult to convey. What exactly does a change of 1ug/dl in the geometric mean of the country with a large gsd imply, particularly when discussing the problem in a local school? Moreover, the health significance of a 1% change in the probability of exceeding a 97.5%-tile blood lead levels is even more difficult to grasp when applied to an immense population that is largely unaffected. This becomes even more confusing given that the method to determine the benchmark level was developed using the observed baseline US water lead distribution and then substituting a point water lead concentration, as opposed to a truncation of the original distribution. This seems to imply in practical terms, that the latter scenario assumes all the nation's children are subjected to the target concentration. Does this

mean the risk communicators' message would be "if all the children in the US had to drink this water, the result would be XXX many more poisoned children." In developing this health criteria, EPA should recognize that the public health representatives will need to convey not only the risk but also EPA's thinking and methodologies that go into the determination and meaning of the criteria.

Since the early days of IEUBK analyses in the Superfund Program, various researchers have advocated developing a probabilistic front-end exposure module for the IEUBK model. Although there has been broad support for continuing to develop these modules for research and academic purposes, this approach, historically, has been rejected as a regulatory tool for a number of reasons. Most criticisms cited the large uncertainties and lack of support data associated with developing distribution variables for the numerous inputs, inherent problems associated with truncation and correlation among the many input distribution variables noted by some public commenters, and the enhanced "opportunity for mischief" by those inclined to manipulate the results. The development of the SHEDS models and publications have notably advanced the development of such probabilistic tools; and EPA has used the model to support risk assessment analyses for other toxins, as noted. However as acknowledged by EPA, Approach 3 does not actually develop a probabilistic front-end exposure module for input to the IEUBK. Rather, Approach 3 might be better described as developing a surrogate biokinetic regression formula emulating IEUBK blood lead predictions as a back-end to the SHEDS exposure model. In attempting to compare the performance of the two models, the inputs to the IEUBK were inappropriately modified to reflect the inherent assumptions of the SHEDS Approach 3, as noted in detail above in response to Question 2.

It seems the most substantial difference in the SHEDS and typical IEUBK analyses is the substitute use of geometric means derived from SHEDS analyses to characterize input values in the IEUBK, reportedly done for comparative purposes. There is little doubt, this greatly changes the predicted blood lead distributions that would otherwise be obtained from the IEUBK model. Although the differences in the diet component should be further examined and discussed, the critical differences are soil/dust ingestion rate, soil/dust lead concentration, and drinking water intake. The current combination of these values input to the IEUBK likely yields spurious results that have little health relevance. This leaves open the question of the health relevance of the SHEDS model results, as it uses the same inputs and yields similar results.

EPA notes in interpreting IEUBK model results:

> "In considering these "individual" approaches, it is important to recall that the output of the IEUBK model may be interpreted as being representative of an individual, or of a group of individuals with identical exposure profiles. The geometric mean BLL represents a singular estimate for the BLL of an individual or identical group, while the BLL distribution represents the range of plausible BLL values and provides the probability of a child or group of children having a BLL above a specified value."

While one might consider changing "identical" to "similarly exposed" and "singular estimate" to "typical or most likely", it is most important to remember that these applications assume logarithmic distributions of the predicted outcome blood lead levels that reflect the nature of the blood lead distribution in observed populations. The distribution of plausible blood lead response is generally characterized by the gsd. There has been considerable debate over the years as to what gsd value should be applied and what it represents. Values as low as 1.4-1.5 have been observed among infants with single exposure source, as noted in this report, and among heavily exposed populations in smelter communities and urban neighborhoods with extremely high blood lead levels in the 1970s. Some populations evaluated with the IEUBK model at hazardous waste sites showed gsd values near 2.0, and EPA has settled on a value of 1.6 in most applications

large as an empirical compromise, that anticipates an arithmetic mean ingestion rate. Because there are few "identically" exposed populations, the 1.6 gsd likely reflects both individual variation across the bio-kinetic responses and measurement error, plus some inherent variation in the exposure variables (i.e., the difference between "identical" and "similarly exposed", which does not fit the classical definition of measurement error).

EPA elected to use geometric mean of 26.6mg/day for all ages and apply a large gsd (3.3?) in Approach 3 to account for the variance in the US population, and applied the same geometric mean value as a point ingestion rate in Approaches 1 and 2, subsequently depending on the 1.6 gsd applied in the following step to account for any variation. The use of the geometric mean likely makes the 1.6 gsd inappropriate, and the resulting blood lead predictions spurious. Although the details of the methodology to calculate 26.6mg/day are not included in the report and don't seem to be apparent in reviewing Ozkaynak et al. (2011), it is assumed that the mean and the probabilistic distribution applied is related to the log normal fit to the model output referenced in Ozkaynak et al. (2011) (35.7mg/day,3.3gsd). The same study shows an arithmetic mean and 95th %tile ingestion rate (68 and 224 mg/day, respectively) similar to other studies, but lower than the EPA Exposure Factors Handbook suggested 100 mg/day default recommendations. EPA assumed the over-predictions by default inputs to the IEUBK are due to overestimation of the ingestion rates. Although this over-prediction of NHANES blood lead levels could, in part, be due to some overestimation of the ingestion rate, it also may result from the simplistic point estimates of soil/dust concentrations that fail to capture the variance in US soil/dust exposures.

The model used to develop the input ingestion rate distribution for Approach 3 includes 20 variables, with 8 distribution forms, and 3 levels of confidence in the supporting data. It is not unexpected that a multiplicative model with these many variables, and some with low levels of support data, would produce large gsds and lower geometric means than indicated in observational studies. Sensitivity analyses conducted in Ozkaynak et al. (2011) show dust loading on carpets, soil skin adherence on hands, number of hand washes/day, and %-floor cover by carpets as the most sensitive variables. The reliability of the distributions of these variables nationally is of some question. Appling the geometric means of national population exposure variable distributions developed in Approach 3 to the IEUBK encompasses large variation in several sources, co-factors, and exposure profiles that likely bring the application of the 1.6 gsd into question. This implies that half of 2-year-old children in the US have ingestion rates lower than 30mg/day, at most scaled up to 80mg/day at +2gsd when applied in the IEUBK. These lower geometric means and high gsd values used by EPA in this report are consistent with some tracer studies as noted in Ozkaynak et al. (2011). It should be noted, however, that the large variation in tracer studies has been a subject of debate for some time and results in ingestion rates that differ substantially from those determined by other methods and those employed in other EPA regulatory applications. Use of these ingestion rates would constitute a major change from current EPA policy in other programs.

Moreover, those most sensitive variables noted in the model-generated ingestion estimates are home and personal hygiene, behavioral, and socio-economic related factors. When combined with the large gsd, those variables could be interpreted as suggesting that lead poisoning problems in the US are confined to a small percentage of the population in extremely dirty homes, with poor housekeeping, hand washing, and bathing practices; while the vast majority of children ingest less soil and dust than previously assumed in regulatory analyses. This could continue to fuel, or reignite, arguments that childhood lead poisoning is a parental and

child behavioral problem, rather than a pollution problem. This argument has largely been refuted by the dramatic decrease in BLLs in children in the US achieved through regulatory actions to reduce lead pollution in their environment.

With regard to Approach 1, or estimating threshold values from the tail of the blood lead distribution, EPA is attempting to apply the IEUBK across the NHANES populations that exhibit much greater gsds, that challenge the assumption of similarly exposed population groups. EPA has, in effect, diluted the tail of the distribution as NHANES purportedly represents tens of millions of children with little or no significant drinking water (or total) exposure in the analyses. This makes the 95% and 97.5%-tile targets arbitrary percentages largely determined by the size of the overall population, rather than identifying those whose risks may not be sufficiently addressed through the standards determined from the central tendency. From a public health perspective, the emphasis should not be on the tens of millions who are safe, but on the hundreds of thousands of children at risk. It is possible that these at-risk children are not found in the tail of a national logarithmic distribution; but may be in a bi-modal distribution, where most US children are protected, and a minority are experiencing different "similarly exposed" scenarios. The pertinent question is how many of these at-risk children can be efficiently protected by lowering the media concentration limit (or some alternate form of household health-based benchmark), or is their exposure due to factors that require additional protective measures? The evaluation of the entire US population as a single distribution may serve to provide perspective on the overall level of protectiveness and residual risk in public water systems; but it provides little assistance in evaluating the efficacy of health-related benchmarks. EPA should consider stratifying the national data bases into similarly exposed sub-groups and analyzing the data with respect to more representative upper limits.

Regarding Approach 2, or calculation of benchmark water concentrations from predicted mean blood lead levels, the report does make comparisons between the predictions of the surrogate IEUBK regression and IEUBK model runs inputting the same absorbed lead into the "Other" intake route of the IEUBK, noting less than 5% differences in results. This result would be expected, but as EPA noted, this occurs after the exposure and absorption modules of the IEUBK and is simply the absorbed lead intake feed to the bio-kinetic module. The regression is similar to the biokinetic module used in the earliest forms of the IEUBK. That was a linear application of the Harley-Kneip (HK) coefficients obtained from controlled absorbed lead dosage of juvenile baboons. The following Table compares the surrogate regression Beta (1) and HK coefficients:

Comparison of IEUBK Surrogate β1 to Original HK Coefficients

Age Interval	Exhibit 36. β1 Value	H-K Coeff.
0.5-1	0.547	- -
1-2	0.447	0.297
2-3	0.379	0.404
3-4	0.355	0.366
4-5	0.336	0.350

5-6	0.313	0.363
6-7	0.288	0.345

The surrogate analyses showed a .995 R-square correlation with IEUBK model runs using the alternate source route, and likely indicates that substitute regression equation accurately predicts the IEUBK biokinetic calculations. However, two questions arise. As EPA notes, the exposure route and absorption components of the IEUBK are not included, limiting the route- specific options in the model. One concern is with respect to use of the "Other" route to evaluate the efficacy of this surrogate method. As EPA notes, use of the alternate pathway option in the IEUBK fixes lead intake over the life of the child, and bypasses the IEUBK capability to assess age-specific exposure considerations. These analyses could be greatly improved by actually developing a probabilistic front-end to the IEUBK providing age and route-specific intakes determined from stratified soil/dust ingestion and concentration partitions input in batch mode.

A second concern is with the disparity in the absorbed lead and blood lead coefficients in the above table for the youngest children. Although, the IEUBK itself may produce the same results, the surrogate coefficients for 1-2-year-old children are much higher than that observed in the original primate studies, and there were no observed data for infants. EPA's modifications for the youngest age group, in both the IEUBK and SHEDS model surrogate equation shows the highest coefficients and would yield the highest blood lead levels for these children. The blood lead predictions for these children are based on EPA theoretical adjustments made to the IEUBK and are substantially higher than H_K observations. Because this age band is a critical population, EPA should acknowledge and discuss the experience, support material, and reliability of the results for this age group in contrast to older children.

One interesting SHEDS findings was that no level of water lead would bring the population below the 97.5% target EBLLs. This should not be regarded as an artifact of the analyses. There are significant numbers of children in the US above these levels due to sources other than water. That Approaches 1 and 2 did not predict these children is, likely, an indicator that the baseline blood lead levels are under-predicted. Some children in the 95th plus percentiles should be predicted by the IEUBK using the 1.6 gsd. These children not showing up in these analyses is an indicator that the baseline estimate is too low; or that the contemporaneous effect of water lead is greater, and would be further underestimated by the reduced consumption rates adopted by EPA in these analyses.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES
Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

In the report, although denying that the EBLL and "target" %-tiles to exceed criteria are not health related, EPA makes the following assertion with regard to Approach 3.

"In addition, population-based approaches are consistent with previous EPA methods for assessing lead exposures."

As noted above, EPA states this is only a statistical exercise, but nevertheless is developing a methodology with profound health implications. This makes it difficult to provide specific comments regarding the inputs to, and interpretations of, the output from these models without substantial caveats. It is also a methodology with a long and sometimes contentious history. A brief review of the evolution of this strategy may help to understand this dilemma with respect to use of current blood lead levels. EPA has used percent to exceed blood lead health criteria in regulatory applications for the past 40 years beginning with the NAAQS in 1977. At that time, the air quality standard was developed with the objective of keeping 95% of children nationally below a 30ug/dL blood lead level. Recognizing the relatively consistent lognormal distribution of blood lead levels in similarly exposed populations, required that the mean national children's blood lead level not exceed 15ug/dL. In EPA's view this allowed an air-sourced increment of 3ug/dL when added to the 12ug/dL national average. EPA's policy at that time was that the 12ug/dL average was due to sources other than air, and that the children in the 95th plus percentiles of the distribution were influenced by exposure co-factors that also could not be mitigated through regulation of air lead levels.

The development of initial IEUBK model by the EPA's Office of Air Quality Planning and Standards (OAQPS) in the mid-1980s was the initial attempt to quantitatively consider multimedia sources and incremental impacts of individual sources on blood lead levels. By this time, the health and scientific community, and the Agency, recognized that irreversible deleterious health effects occurred at lower levels than previously detected; that the log normal characteristics of the population blood lead distributions were (in part) due to multiplicative effects of intake rates and exposure co-factors; and the dose-response was non-linear. By 1984, the blood lead health criteria were lowered to 25ug/dL, a level no individual child should exceed. However, the EPA regulatory approach continued to apply this target to 95% of the population, as it was believed that the blood lead levels of children in the upper percentiles could not be effectively addressed by further reducing media concentrations, again as the high intake and absorption rates were due to exposure co-factors; and those co-factors were often related to peculiar behavioral or socio-economic conditions. By 1991, the IEUBK was being applied in risk assessment and mitigation efforts in other Agency programs and the operative blood lead criteria was 10ug/dL for 95% of the population with no child exceeding 15ug/dL. The CDC directive on which EPA relied indicated adverse effects of lead occur at blood lead levels at least as low as 10 µg/dL; but a blood lead level < 10 µg/dL was not considered to be indicative of lead poisoning. CDC also indicated that it was unlikely that single media sources of blood lead levels in the 10-14ug/dL could be identified and remediated (i.e., lead concentration reduced) to mitigate the risk; and that intervention and counseling efforts to modify behavioral and socio-economic considerations should be applied.

It followed that over the next decade the risk mitigation strategies developed at many EPA CERCLA and RCRA program sites employed a dual strategy of (i) reducing media concentrations to effect lower mean blood lead levels that would result in 95% of children having a predicted blood lead level below 10ug/dL and (ii) a concurrent lead health intervention program to effect beneficial behavioral modifications for families with children above 10ug/dL and medical intervention for children above 15ug/dL. The IEUBK was extensively used in both risk assessment and mitigation, particularly for identifying media specific cleanup criteria (or media concentration levels). In later years, the EPA modified the IEUBK risk analyses to require a 95% probability of a blood lead level <10ug/dL for each individual child in a population, as opposed to 95% of the entire childhood population. This resulted in significantly more stringent cleanup levels (i.e., it required lower media concentrations), as the percentile now applied within the most vulnerable age groups of 2-3-year age children, not across the 1-7-year age population originally evaluated.

This EPA policy history is important to consider in light of the perceived eventual use of the "percent to exceed health criteria" from the proposed IEUBK drinking water models in comparison to current blood lead levels. In past applications, EPA has used the 95th percentile of the blood lead distribution to define the maximum allowable media concentrations necessary to lower the central tendency (or population mean blood lead level). This document does the same, but asserts it is to accommodate observed 97.5% upper limits of the NHANES populations, as opposed to health criteria. This is accomplished by recognizing the log normal characteristics of the response variable and applying the appropriate geometric standard deviation (gsd). Implicit in the EPAs historic approach (and perhaps not acknowledged in this report) is that the risks to the 5% exceeding the blood lead criteria are not efficiently, nor sufficiently, addressed by further lowering the media concentrations (i.e., the "tail" is excluded from determining the standard). The modeling strategies proposed in this review, however, seem to suggest that the analyses are being driven by trying to fit the 97.5%-tile of the NHANES population, and that responses within the "tail" have been used to modify the input parameters, and ultimately determine the appropriate media concentrations. Several Public Comments noted the uncertainty, lack of reliability, and sensitivity of these high percentile blood lead estimates and subsequently the target "health based benchmark, or household action level" drinking water action levels derived from the tail of the distribution. This report suggests an underlying objective of modifying these evolved risk assessment methodologies is to fit the tail of large national data bases collected and assembled for other purposes by diverse methodologies. Additionally, the inclusion of the soil/dust ingestion rate distribution with a large gsd derived from a behavioral modeling study required using a low geometric mean central tendency value that corrupted the Approach 1 and 2 results. One can't resist pointing out this may represent a classic case of "the tail wagging the dog".

If the history of the distributional aspects of blood lead reduction in the US over the past decades is any indication, regulating concentrations in any environmental source media can have a significant effect on reducing blood lead levels for about 90-95% of the children in the contemporaneous distribution. The children in the higher percentiles suffer multiple atypical source and exposure co-factors, that cannot be remedied by further reductions in that media concentration. On the bright side, history also shows that effecting source reductions in one medium shifts the national blood lead distribution, making it possible to achieve further reductions by addressing other media, bringing more children in the tail below the threshold criteria. Unfortunately, there is no safe threshold and this trend will continue until zero blood lead and near zero (perhaps requiring pre-industrial geologic background levels for environmental media.

Perhaps, now it is the safe drinking water program's turn to shift the distribution. EPA's task should be to identify and implement that combination of source control (health benchmark) and affected population that maximizes protectiveness. And, at the same time EPA should identify those remaining victims of lead poisoned children that responsible public health practice obliges civilized societies to address through other intervention strategies.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques.?

Improvements: Approaches 1 and 2 could be improved and made health-relevant by using more appropriate consumption input parameters and applying these to stratified exposure scenarios that reflect more

sophisticated soil/dust concentration profiles with both home and community partition components. Ingestion rates could be increased to levels reflective of the more recent literature. Committees currently evaluating ingestion rate recommendations for the IEUBK and Exposure Factors Handbook should be consulted. Geometric means should not be considered without careful examination and probable readjustment of the biokinetic and distributional components of the IEUBK. Although soil dust data may be difficult to obtain and organized, modeled estimates based on variables in addition to house age would improve the analyses over the simple point estimates applied in this report. The soil and dust concentrations should be developed by combining home, yard, neighborhood and community-wide characteristics. It would be best to enter these soil/dust exposure profiles to the IEUBK in batch mode, in proportion to the abundance of each exposure stratification in the US population (or NHANES database) for comparative purposes.

The drinking water consumption rate conflicts with those used in other programs and should be resolved. An Agency-wide supported value(s) should be used, as the determination of the appropriate benchmark will be directly proportional to the consumption rate value. The results of Approaches 1 and 2 could also be presented in terms of the stratified analyses to examine the impact of different drinking water concentration levels among diversely exposed communities in the US.

The SHEDS analyses could be amplified to include alternative distributions of ingestion rates, and the results examined through sensitivity analyses assessing the impact of other input variables in explaining apparent over-prediction of blood lead predictions with the NHANES database. Additional sensitivity analyses should be run on combinations of consumption variables and concentration profiles. More sophisticated media concentrations should be developed and sensitivity to various elements of these distributions should be conducted.

Variability in drinking water data (homes vs systems): More detail should be provided regarding the frequency and magnitude of elevated water concentrations and the relation to exceedances of the action level (AL) and water purveyor's monitoring and follow-up requirements. The Benchmark should be developed within the context of the AL. High values observed in distribution systems should be investigated and permanent solutions encouraged or required; and periodic lowering of the AL should be considered as water systems evolve, older lines are replaced. The Benchmark should be developed to allow users to weigh the health risks of elevated water concentrations in their homes and schools in their own communities against the health benefits and costs of corrective actions. The Benchmark values derived from any of the approaches will inherently reflect the exposure periods anticipated in the IEUBK model. Formally, these exposure estimates assume a series of lifetime annual averages to accommodate the yearly blood lead estimates provided. Practically, blood lead levels for young children reflect recent absorption likely on the order of months to, perhaps, a year. EPA appropriately used the 30-day exposure averaging time noting recommendations of an external peer consultation panel. Thus, the benchmarks should reflect some type of rolling average on the order of 30 days to a year. The difficulty, as several public commenters noted, is that these values cannot readily be compared to typical water testing results reported by utilities or schools. Single high values encountered in routine monitoring are not uncommon; but a series of follow-up negative samples is not sufficient to make determinations regarding compliance with longer demand weighted averages. Sampling at individual service taps is so infrequent that most excursions to high levels will go undetected.

The frequency of sampling required to obtain reliable 30-day rolling averages for each exceedance would be a waste of resources and an impossible burden. As a result, EPA could consider a monitoring scheme that requires periodic representative sampling of stratified exposure scenarios based on risk co-factors known to effect high lead levels (e.g., age of housing, corrosive water, lead service connections, quality of infrastructure, etc.). If high levels are encountered, protocols for follow-up in similar communities could be developed. Because a single high value reported can be cause for family and community concern, a compositing protocol for follow-up on high values should be required, designed to both obtain reliable demand-related average concentrations, and confidence among users.

EPA should consider pilot studies in high-risk communities exhibiting fluctuating water lead levels at a substantial percentage of community taps. These pilot studies should address both a survey technique to identify the frequency of excursions in a community, and appropriate follow-up strategies to develop reliable average concentration estimates, and provision of alternate water supplies, if required.

COMMENTS SUBMITTED BY

Anne Loccisano, Ph.D.

External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Life stages: The age groups generally seem appropriate, but there should be more of a break-down with the 0-7 years (i.e., 2-3 years, 4-5 years, etc). The 0-7 years life stage is of particular concern as this is a broad time span. EPA obviously understands that 0-6 months differs from 1-2 years as they have already broken out these time periods, but exposures over this broad time span of 0-7 years will be very different as children are developing rapidly and their behaviors will change. However, this broad time span may be useful for evaluation of cumulative exposure that may influence long-term neurodevelopment. Fetal exposure should also be considered. The IEUBK model is limited in its ability to model this life stage but this should not preclude EPA from doing so. A physiologically based pharmacokinetic model would allow for examination of maternal, fetal, and infant exposures (from breast milk). A PBPK model could also be extended to allow for modeling of childhood exposures and would allow for incorporation of variability in both exposure and biokinetic parameters.

Several studies[1] have reported on delayed puberty in girls being associated with elevated BLLs. This is another endpoint that should be considered in the modeling approaches, so extending the modeling efforts to include this life stage would add utility (while the IEUBK model considers children only up to age 7, a PBPK model could be used to examine girls around 12 years of age). I do not know if the elevated BLLs reported in these studies were associated with exposure during the 0-7-year life stage, but modeling girls around the age of puberty to examine how their BLLs are affected by lead in drinking water (as well as other sources) may be informative.

Exposure scenarios—drinking water only: Since the focus of this effort is to develop drinking water standards, I think presenting the results from a drinking water only scenario is helpful. Although this is likely not realistic (exposure will come from other sources and it is unlikely that the baseline BLL will be zero), this scenario would be useful in evaluating how incremental changes in lead water levels will affect the baseline BLL. This scenario would probably also be applicable to the 0-6-month life stage for formula-fed kids, where most exposure would come from tap water.

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[1] N Engl J Med. 2003 Apr 17;348(16):1527-36. **Blood lead concentration and delayed puberty in girls.** Selevan SG[1], Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J.

Environ Health Perspect. 2010 Dec;118(12):a542. doi: 10.1289/ehp.118-a542b. **Do metals meddle with puberty in girls? Lead, cadmium, and altered hormone levels.** Betts KS.

Environ Health Perspect. 2003 May;111(5):737-41. **Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994.** Wu T[1], Buck GM, Mendola P.

All pathways: This is the most useful scenario as most children will likely have multiple exposure sources (and some will have greater exposure from soil or dust than water) and the contributions of each of these to the overall BLL should be evaluated.

Maternal blood lead should be given more consideration as this will obviously affect the baseline BLL in the child.

Target BLLs: The consideration of the two BLLs is reasonable; these are the current CDC criteria for elevated BLLs. As this effort is concerned with developing drinking water standards, it is important to understand how changes in water lead concentrations will affect these baselines BLLs.

While the analysis of the probability of exceeding this level is useful (Approach 1), I think it is more useful to understand how water levels will incrementally increase the baseline BLL (Approach 2). Approach 1 is supposed to answer the question of what Pb water concentration will increase a child's probability of having an elevated BLL. Any increase in exposure above the baseline BLL will increase the probability of having an elevated BLL; it just seems more practical to evaluate the increase in BLL resulting from various water concentrations of lead.

Another approach that may add utility is to run the models using "feasible" or "target" water lead concentrations to examine how these affect the BLLs (as well as varying the baseline contributions to overall lead exposure). Also, it would be helpful to run these models with a specified population (i.e., one that has higher exposure from water—for example, homes that have lead-based paint are also likely to have higher lead levels in soil/dust and drinking water) so examining the model outputs for these special populations might be useful. When more data become available for homes/schools with lead service lines (and also on how seasonal variability in lead concentrations affect the home/school concentrations and thus exposures), these data should be incorporated in order to understand how this will affect the child's BLL. A "worst-case" scenario should also be evaluated (i.e., highest soil/dust/food concentrations along with high water concentrations) in order to understand the risk that this could pose to a highly exposed child.

As lead concentrations in water are transient, an additional approach that might be useful is to model varying periods of time (24 hrs, 1-2 months, and 6 months to a year) and then compare the results and how the changes in lead concentration over time affect the BLL.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

Model inputs appear to be reasonable as they are based on data (and IEUBK model parameters are not simply fitted to data). However, correlation between input parameters (both the pharmacokinetic parameters in the IEUBK model and exposure inputs) should be assessed, as this will obviously affect model output.

Use of NHANES data for water consumption: As stated in the draft report, there are no drinking water intake values specific to formula-fed infants in the NHANES data that are used in the SHEDS model; thus, the population that the NDWAC suggested for consideration is not considered in Approach 3. I understand that the NHANES data were used in order to ensure consistency between the IEUBK and SHEDS analyses; however, these data are quite different than those in the Exposure Factors Handbook (EFH). The EFH values should also be tested to examine how those affect model output.

In addition to the water intake parameters, other parameter values used in this effort are different from those recommended by EPA for use in the IEUBK model and also different from those in the Exposure Factors Handbook. Although the draft report justifies use of values different from recommended values, EPA should consider the fact there should be consistency across the Agency when recommending parameters to be used for risk assessment purposes. As with the water intake parameters, the models should be run with the recommended/default parameters in order to examine how this affects model output.

Model inputs should consider additional variability—i.e., in pharmacokinetic and metabolic parameters. The IEUBK model uses point estimates for model inputs; these inputs could be sampled from a distribution using a PBPK model combined with Monte Carlo analysis.

I will defer to other experts on the panel who are more familiar with soil and dust ingestion rates and variability in lead water concentrations.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

- **a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.**
- **b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.**
- **c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).**

I understand that the IEUBK model is EPA's standard approach to lead modeling in children, it has been through peer review, and that revisions have been made based on recommendations from review panels. The strength of the IEUBK model is that it is easy to use; however, since the IEUBK uses point estimates as input parameters, variability is not accounted for here, but rather variability is accounted for by use of the GSD (1.6) for BLLs. A potential useful (alternative) approach to use of the IEUBK model would be the use of a physiologically-based pharmacokinetic model, such as the O'Flaherty lead model2, which is capable of examining BLLs associated with different exposure sources. Use of this model would permit a Monte Carlo approach, where variability in both biological parameters (physiology and pharmacokinetics) and exposure parameters could be varied during different life stages (while accounting for correlations between variables). This would allow for the examination of variability in BLLs resulting from differences in physiology and exposure. This would also allow for examination of the contribution of various exposure sources to BLLs. The SHEDS model could also be coupled with the PBPK model (as has been done with permethrin and arsenic).[3]

Approach 3 seems to be the best out of the 3; this is a probabilistic approach and is thus more scientifically sound and seems to be in line with how EPA approaches probabilistic risk assessment in other areas (e.g., pesticides). However, a more straightforward approach would be to directly link the IEUBK and SHEDS models rather than use of regression equations. If the regression approach is used, this should be justified and explained more clearly.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

Sensitivity analyses should be conducted for all parts of modeling (physiological, pharmacokinetic, and exposure parameters). Local analysis will address sensitivity relative to point estimates of parameter values and global analysis will address sensitivity relative to the entire parameter distribution. Sensitivity analysis will obviously identify which parameters have the greatest impact on model output, and if those parameters have significant uncertainty associated with them, those can be focused on for refinement. In approach 3, the sensitivity analyses appear to be conducted for only the media concentrations of lead (water Pb, soil Pb, etc), ingestion rates, and absorption rates; it is not clear to me if other parameters were varied and the model output was examined for these. As stated above, sensitivity analyses should be carried out for all

[2] O'Flaherty, EJ 1998. A physiologically based kinetic model for lead in children and adults. Environ Health Perspec, 106 (Suppl), 1495-1503.

[3] Toxicol Sci. 2012 Nov;130(1):33-47. doi: 10.1093/toxsci/kfs236. Epub 2012 Aug 1. **A pharmacokinetic model of cis- and trans-permethrin disposition in rats and humans with aggregate exposure application.** Tornero-Velez R[1], Davis J, Scollon EJ, Starr JM, Setzer RW, Goldsmith MR, Chang DT, Xue J, Zartarian V, DeVito MJ, Hughes MF.
Environ Health Perspect. 2010 Mar;118(3):345-50. doi: 10.1289/ehp.0901205. **Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 2003-2004 NHANES Data.** Xue J[1], Zartarian V, Wang SW, Liu SV, Georgopoulos P.

Environ Health Perspect. 2003 May;111(5):737-41. **Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994.** Wu T[1], Buck GM, Mendola P.

model parameters. Also, sensitivity analysis should be conducted with the maternal BLL as this will ultimately affect the child's baseline BLL.

NHANES BLL data are comprehensive so this is a reasonable data set for use in model validation and also for establishing baseline BLLs. However, there are other BLL data available (such as NHEXAS and probably other federal and state data); all three approaches should be run against these other data sets for validation. Obviously, if the model yields satisfactory predictions for multiple data sets, confidence in the approach is increased. If local data from a highly exposed community are available, this would be useful in establishing baseline BLLs for that particular area.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

Each approach has utility in that they all address different questions. Approaches 1 and 2 are similar in that they both use the IEUBK model alone and examine a "representative child". Approach 3 is a probabilistic approach in that the SHEDS model is used, but as only variability in exposure (and not physiological/ biological variability) is considered, I do not consider this a truly probabilistic approach. As someone who regularly does simulation/modeling work, I prefer Approach 3. However, although each approach can help inform risk assessments by providing different information, I do not think that any of these approaches can really be used alone.

In order to incorporate variability (in water concentrations, other environmental media concentrations, and biological variability), a PBPK model coupled with Monte Carlo analyses could be used. A model like this will be more complex, but code for various lead PBPK models is available, can easily be implemented at EPA, and can better address variability and uncertainty.

While the IEUBK model is easy to use, it is a "black box"; many parameters are fixed and the source code cannot be modified by the user. Models such as the Leggett, Rabinowitz, or O'Flaherty models can be modified by the user, which makes them much more transparent and allows for more flexibility in parameter values. Also, with model validation, the code can be modified in order to update biological processes (absorption, distribution, etc.) that describe the disposition of lead in the blood and other tissues in order to better describe the validation data (I am not saying the model should be modified in order to simply fit the data here, but if new information becomes available on kinetics, that can be incorporated into the model code).

COMMENTS SUBMITTED BY

Marc A. Nascarella, Ph.D.

External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

GENERAL COMMENTS

1. Overall EPA has described three approaches that are rigorous, credible, and represent a significant body of work to inform the future regulation of lead in drinking water. While there appears to be several opportunities to refine or clarify important aspects of each of the presented approaches, the proposed technical framework is a valuable resource and should be given thoughtful consideration in any future water quality policy deliberations.

2. As presented, the approach lacks sufficient clarity in both how it will be applied to regulating drinking water, and how it should be interpreted from a health-based perspective. Left unchanged, this will serve to add confusion to an already exceedingly difficult conversation about lead in drinking water. Importantly, it will also run counter to the primary goal of this endeavor - an analysis to inform public education requirements, and risk mitigation actions at the household or school level. Any final approach should be presented and performed in a manner that will provide very *clear* communication on the *health-based* regulation of lead in drinking water.

3. No safe level of lead has been identified and all sources of lead exposure should be eliminated. The reviewed document, however, ignores the significant role of deteriorated lead-based paint and the resulting dust and soil contamination as a source of lead exposure responsible for increases in blood lead levels in young children. This concept is not adequately explained or examined in the document and has the potential to divert significant attention away from a very important public health issue – exposure to lead-based paint.

4. The estimate of exposure to lead from water in each scenario requires further explanation. Given this nature of lead release in drinking water supplies, it seems appropriate to better characterize how the exposure model averaging times (biological exposure averaging) account for this, and how the differences in the dose-response relationship of acute exposure (24 hours or less), short-term exposure (1-30 days), and long-term exposure (more than 30 days) are accounted for. Each scenario may present a different type of exposure, associated with a different hazard (or biological effect), and will result in different risks.

5. The IEUBK model seems ill advised for applications where exposure periods are less than three months, or when high exposure occurs less than one per week or varies irregularly. The EPA modeling approaches in the subject document does not seem to be consistent with this application.

6. As regard to the specific application of the approaches, EPA must describe both the risk-based interpretation of blood lead levels (in terms of how they relate to a "critical effect", as defined in a regulatory toxicology context), and very clearly describe how this relates to the regulatory application to a corresponding level of lead in water (in a risk communication context). For example, the described approach does not make clear what an appropriate health-based effect should be? EPA should specifically discuss the risk management rationale to establish this as a "critical effect" and how this relates to a *Health-Based Benchmark*.

SPECIFIC COMMENTS

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 µg/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

RESPONSE

The *age* range is generally appropriate (infants to 7-year-old children). Formula-fed infants are the most susceptible population, and this life stage is sufficiently captured using the presented approaches.

The document should describe, in a quantitative manner consistent with the currently presented analyses, why pregnant women and fetal exposure (from maternal lead) is not otherwise considered. At relatively low levels of maternal exposure, lead is associated with hypertension, premature delivery, and spontaneous abortion. While the IEUBK model is limited in the ability to model this scenario, this should not preclude its consideration. It did not preclude the use of the Adult Lead Model.

It may be useful to develop specific guidance for exceedances at schools (i.e., consider children > 5 years old). In this specific guidance, considerations should be given to the fact that total water consumed at schools is roughly 50% of that of residential use. The analyses should be conducted in a manner to consider elevations of water lead levels at specific taps. For example, an approach that describes how a fraction of the total daily consumption of water (~0.15L), might compare to an estimate derived from consuming all water (~ 0.600L) from one source might be useful.

The approach to use *target* BLLs in the manner described is confusing. As presented, this outcome is neither "health-based" nor a true benchmark. Biomonitoring of lead in blood are measures of *exposure*, not measures of *health effects*. Additionally, the term benchmark has been widely adopted as a term that refers to a dose-response modeling approach to estimate a point of departure, upon which to base a health-based criterion. To use the term *benchmark* here implies that 3.5 µg/dL or 5 µg/dL is a *benchmark response* that corresponds to a *benchmark concentration* of lead in water. This adds confusion to an already exceedingly difficult conversation about lead in drinking water, and will serve to distract from the goals of this endeavor (an analysis to inform public education requirements, and risk mitigation actions at the household or school level). Further discussion on this point follows in more general comments.

As blood lead levels are not measures of "effect", the upper tail(s) of the distribution of NHANES data describing blood lead levels should not be interpreted as a health-based criterion or "targets". These are exposure measurements and not health-based thresholds of effect. As the EPA modeled approach is focused on shifting a "baseline probability distribution of blood lead for an individual", the sensitivity of selecting the tails of this distribution (3.5 and 5.0 g/L) and not a central tendency estimate should be explored.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

RESPONSE

The input parameters for both the point estimate and distribution of water lead levels need further explanation. The report characterizes that public drinking water supplies are unlikely to have lead present at the source (p. 9), and water becomes contaminated due to the presence of lead pipes (i.e., lead service lines) or leaded plumbing parts (i.e., fixtures, solder, fittings). Given this characterization, when lead is measured in "first-draw" water, it is likely to be measured as a transient elevation, as a result of changes in water flow (i.e., particulate release or a bolus of stagnating water). Given this nature of lead release in drinking water supplies, it seems appropriate to present approaches to modeling the dose-response relationship that account for periods of acute exposure (24 hours or less), short-term exposure (1-30 days), and long-term exposure (more than 30 days).

The presented approaches do not seem to account for these conditions in either the exposure assessment or the characterization of the response. Additional effort should be made to characterize a level of lead exposure that accounts for this potentially sinusoidal pattern of exposure, and the resultant physiological impact of transient acute exposures to particulate-related spikes in Pb water concentrations, coupled with consistently elevated levels of lead (sometimes occurring simultaneously), as well as lead-free water.

I found the section on Maternal Blood Lead (Section 5.10) confusing. The section begins by describing how the mean BLL for women of childbearing age was estimated using data from NHANES using the 2011-2012 and 2013-2014 survey years (n = 2,003). EPA pooled data files across the two survey cycles to create a 4-year dataset representative of the U.S. civilian, non-institutionalized population. The description of the age criteria for entry into this pool is written in a confusing manner, as it seems to imply that only parous women were included - i.e., "blood lead data were collected for all participants aged 1-11 years old." It is unclear why pooled analyses of *women of childbearing age* would consider the age of children.

As regard to this specific parameter, the definition of women of childbearing age (i.e., 18-45 years) seems restrictive. I would suggest evaluating the sensitivity of this assumption to both a broader definition of "childbearing age" – to align with biological capability – perhaps begin at 15 years old (Johnson et al., 2006). I would also evaluate model estimates based on sensitivity to a parameter based on current trends, suggesting that mothers are typically older (CDC, 2017). These older individuals may have higher BLLs.

The use of the IEUBK requires that the user specify a compartmental lead mass at "initiation" (simulated birth) for an exposed child. The model assumes that the blood lead concentration of this day 1 newborn child is 85% of the maternal blood lead concentration. This underscores the need for more details on the rationale to include a geometric mean BLL of 0.61 (SE = 1.02) µg/dL as default assumption on mother's blood

lead concentration[1]. This seems very low, especially compared to the published geometric mean BLL of group such as Asians, reported as 1.15 µg/dL (NHANES, 2011-2012 survey years).

It is noteworthy that the lower limit of detection (LLOD) in the NHANES data is different between the 2011-2012 and 2013-2014 survey years. For example, the LLOD for lead in blood in the 2011-2012 survey years is 0.25 ug/dL; compared to a LLOD for the 2013-2014 years of 0.07 ug/dL. This is a 3.5-fold decrease. Said differently, this is a 3.5-fold increase in the analytical ability to detect lead in a sample of blood. As regard to the approach for calculating aggregate results, if a measured value is below the limit of detection, the CDC analytic guidelines prescribe that you impute a value. For analytes with results below the LLOD, an imputed fill value equal to the LLOD divided by the square root of 2 (LLOD/sqrt[2]) is used (CDC, 2016). The clarification of this calculation should also describe how many blood lead measurements were actually available (N missing), and how this relates to the survey weights and representativeness of the U.S. population of women of childbearing age. As any of the EPA modeled approaches appear sensitive to this estimate, the sensitivity of the calculation of the new maternal blood lead calculation should be explored.

It is unclear why the water consumption rate is based on NHANES data, and not more typical data such as the Exposure Factor Handbook or World Health Organization default data. It is also not clear to what extent EPA considered the alternative water model (IEUBK Equation E-6b; INWATER(t)). This value is calculated as the product of the water consumption rate, and a lead concentration that is calculated as a weighted average of the user-specified constant value as well as values from the home first-draw (FirstDrawConc), a flushed faucet at home (HomeFlushedConc), and a water fountain outside the home (FountainConc).

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 ug/dL or 1 ug/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated

[1] Of note, Page 3 of the supplemental material in Zartarian et al. (In Press) manuscript describes an assumption of "maternal blood lead of 1 µg/dL". This too is confusing and I am unsure when the assumed maternal BLL being used is 0.61 and when it is 1.0.

with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

RESPONSE

The IEUBK model is supported by US EPA guidance that specifically states that the model should not be used for (a) exposure periods of less than three months or when (b) high exposure occurs less than one per week or varies irregularly. This is fundamental to the use of this model, as the IEUBK is based on a central premise that steady-state exposure can be understood through movement of environmental lead, mediated by a blood/plasma compartment. The IEUBK is essentially a model of plasma exchange, with the long-term lead-binding constituents of the skeleton. In fact, the IEUBK Model has been designed and validated to model the physiological effects of lead over relatively steady-state exposure conditions (i.e., chronic exposure). The EPA application in the subject document does not seem to be consistent with this application.

The nature of lead release in drinking water supplies is so highly variable that it presents acute, short-term, and long-term exposure conditions – in addition to true chronic conditions. EPA should describe how the approaches constitute a steady-state exposure condition, consistent with the application of this model. This is fundamental to the use of this model, as the IEUBK is based on a central premise that steady-state exposure can be understood through movement of environmental lead, mediated by a blood/plasma compartment. The IEUBK is essentially a model of plasma exchange, with the long-term lead-binding constituents of the skeleton.

As regard to specific comments, Approach 1 is focused on estimating a fraction of individuals that can be identified where elevated water lead levels will increase the probability of an elevated BLL by 1% or 5%. I am not aware of a risk-based interpretation of a level of lead in drinking water that results in a probability of a BLL being increased by 1 or 5%. A physiologically relevant health-based interpretation of a 1 or 5% shift is needed. The approach does not make clear what an appropriate baseline BLL should be. EPA should specifically discuss the rationale to establish a baseline BLL.

Approach 2 is focused on identifying a concentration of lead in drinking water that shifts the geometric mean blood lead level by a defined amount. This approach, in theory seems more credible. However, this approach presupposes that a baseline BLL may be calculated assuming only the ingestion of Pb in water. This is both unrealistic, and not sufficiently conservative.

Both Approach 1 and 2 seem to blur the distinction that the goal of the IEUBK model is not to align a “target BLL” to a specific child, but rather predict an average PbB (blood lead) concentration, or the probability that a child with a very specific exposure scenario would have an elevated PbB. Due to the kinetics of lead retention, distribution, and absorption, the proposed metrics do not appear to be appropriate *per se* “targets” when used in this manner. For example, an individual with an existing high blood lead level that is exposed to additional lead from drinking water may have a negligible increase in measurable blood lead (or % increase). For this individual, the lead may cycle/move from the blood to the bone (trabecular and cortical) as well as the kidney, liver, and other soft tissue and organs.

It would be worthwhile to evaluate the IEUBK model parameters quantitatively (perhaps using a Bayesian approach that is similar to the one employed for the exposure inputs). Regardless of final approach, the IEUBK parameters should be more fully explored in terms of key parameters – such as blood to bone transfer and storage in infants. As the excretion of lead in the most sensitive population (infants) is very poorly understood, this appears to be a clear weakness of all modeled approaches that needs to be resolved. This may be significant as even the IEUBK model parameters set Pb excretory rates at the high end of values deemed plausible. A detailed review of intake or absorption values, as well as excretory parameters is warranted. Not otherwise discussed or considered is how the NHANES urinary lead levels in children may be used to consider variations in excretion, and may serve to inform model excretory parameters. While these data are not available for children 5 and younger, an analysis of existing data may have substantial impact on model predictions.

The third approach, a hybrid of a probabilistic exposure assessment coupled to the IEUBK model seems most reasonable. Although, further explanations are needed as to the decisions (or empirical basis) to specify distributions for input variables, specify the model correlation structure, time steps, and the variance in BLLs. Additional analyses should consider an approach that takes full advantage of both IEUBK and SHEDS. For example, SHEDS could be used to predict various distributions from NHANES, and these could be used as IEUBK model inputs. This approach would take full advantage of both models, and limit the limitation of each. Using the current approach, a probability-based approach to estimate exposure, may not adequately address exposure in individuals exposed to high levels of lead, and the use of only an IEUBK-derived "analytical solution" (a polynomial regression equation, and not the compartmental model) fails to take full advantage of the power of IEUBK to consider the kinetics of this type of lead exposure. Given the saturable and non-saturable absorption of lead, the individual parameters may have significant effects on the disposition of lead – especially in an infant.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

RESPONSE

The description of blood lead levels in this document seems to ignore the fact that lead-based paint is the primary source of lead exposure for young children. The dominance of this exposure pathway is complicated to communicate alongside a message that all lead exposure for children should not be controlled or eliminated. No safe level of lead has been identified and all sources of lead exposure should be eliminated. This concept is not adequately explained in the document, and has the potential to divert significant resources and attention away from a very important public health issue – homes containing lead paint. This will add confusion to existing public health-focused efforts in communities of high risk of childhood lead poisoning, and distract from risk communication and risk mitigation actions at the household and school level.

There are many local, state and federal sources of information that would support a robust analysis of the sensitivity of the contribution of environmental media to elevated BLLs. For example, CDC has been collecting blood lead data on children since 1997 and maintains an extensive database. In fact, about 2.5 million blood lead tests are received by CDC each year. While these data are fundamentally different than the NHANES population-based health study designed to assess all children in the United States, these Childhood Lead Poisoning Prevention Program (CLPPP) data should be more fully explored. For example, EPA should consider how combining CLPPP data from different sources, at various levels of geographic and temporal specificity, may inform an assessment of how to accurately "target" a candidate BLL (or percentile/ central tendency estimate), such that a change in water lead level may have meaningful impact on lowering BLLs. Data to support this type of study are available from a variety of CLPPP data sources (CDC, 2013). Previous analyses have shown significant departures from NHANES estimates. For example, approximately 11,000 higher-risk children and adolescents tested at an urban medical center had significantly higher BLLs than the corresponding NHANES references values with a geometric mean BLL of 3.2 µg/dL in males and 3.0 µg/dL in females (Soldin et al., 2003).

The absorption of lead from the gastrointestinal tract will vary depending on the contents of the stomach. A better description of how food in the stomach was considered in the model scenarios is important. As a 90% bioavailability for fasting children is not unreasonable, the sensitivity of the model to this consideration is important. A sensitivity analysis should also be performed on the water ingestion rate for infants, specifically the sensitivity of the model to estimates such as 0.526 vs. 0.64 L/day.

The sensitivity of the models to the maternal blood lead level should be evaluated. For example, I would evaluate the sensitivity of this assumption to both a broader definition of "childbearing age" – to align with biological capability – perhaps begin at 15 years old (Johnson et al., 2006). I would also evaluate the sensitivity to an estimate that captures the fact that mothers are now typically older (see National Vital Statistics System and National Survey of Family Growth data; for examples see CDC, 2017).

The approaches rely heavily on the IEUBK Model. This model's principal application is to model the physiological effects of lead exposure where there are long periods of relatively steady-state exposure. This is based on the assumption that equilibrated blood lead levels after chronic intake are associated with certain toxic effects. Certainly, any approach that will be used to revise the current lead regulations needs to consider this type of steady-state (chronic) exposure, as well as the transient exposures to high levels of lead (presumably from particulate-related spikes in Pb water concentrations). The model needs to be evaluated in terms of the uncertainty of this exposure parameter. As described above, any proposed approach, needs to be evaluated in terms of the sensitivity to changes in the IEUBK parameters. Many of these parameters will also require an uncertainty analyses (bone transfer kinetics).

The approaches could also be improved by a detailed analysis of the voluntary water quality data that has been generated since the revised Drinking Water Action Plan in November 2016. A tremendous amount of public data are now available to better understand the variability of lead levels in drinking water within entire distribution systems. Certainly, much of these data (worst case "first draw" values) could be considered in the IEUBK model as part of an option for the user to specify a first-draw on a home faucet or school water fountain (e.g., Equation E-6 in IEUBK – FirstDrawConc).

5. OVERALL IMPROVEMENT RECCOMENDATIONS

How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

RESPONSE

It is clear that the overarching EPA policy is that the safe level of lead is zero, and the EPA Office of Water will continue to communicate to states, drinking water systems, and the public that the goal (MCLG) is to have a "safe" level of zero lead in drinking water. As this is an aspirational goal, the modeling approaches were reportedly developed to provide states, public water systems (PWS), and the public with a greater understanding of the potential health implications when levels of lead are identified in drinking water. As such, all of the presented approaches, at a minimum, need to be improved if they are to be used to inform public education requirements, prioritization of households for lead service line replacement, or other risk mitigation actions at the household or school level. For example, Approach 1, uses as a health-based benchmark a "1% or 5% increase in probability" of having an elevated BLL and Approach 2 uses an increase of 0.5 or 1 µg/dL as the health-based benchmark. It is not clear to me how EPA would describe the health bases for these particular metrics? Are these increases in a meaningful health-based outcome (e.g., an equilibrated BLL that would lead to an adverse impact such as an IQ deficit)? As a very practical and important matter, how would one begin to describe to a group of very concerned parents that their child's exposure to lead will result in a 1% increase in the probability of having an elevated blood lead level?

Failure to adopt an approach that can adequately explain this fundamental question has the potential to divert significant attention away from a very important public health issue – childhood exposure to deteriorated lead paint, and the resulting dust and soil. This is because a blood lead based approach, if not properly communicated, will confuse and conflate childhood lead poisoning with lead in drinking water. For example, a highly probable scenario is one where a very concerned parent, one whom just learned that their child's exposure to lead will result in the "probability of having an elevated blood lead level" will immediately proceed to have their child's blood lead tested (or request it from a municipality/physician/state/federal agency)? If that value comes back high (i.e., 5 or 10 µg/dL), I suspect that the parent may immediately ascribe that elevation to the drinking water exceedance that they were just notified about. EPA should be mindful of how any final approach can be explained in this scenario. Is an elevated level of lead in water what EPA would describe as the most likely contributor to a blood lead level? Is a public health intervention focused on reducing exposure to water that has the "probability of resulting in an elevated blood lead level" going to provide a meaningful change in an individual's blood lead level? Will it provide a change in a population estimate?

Some considerations when refining the presented approaches are listed in the bullets below.

- An effective communication plan that addresses the complexity of this issue is paramount when seeking to address public concerns. When communicating exceedances of the current (non-health-based) lead action level (15 µg/L), the current health-based paradigm of "no safe level of lead" is often misunderstood to mean "any level of lead exposure is going to cause me harm". As the current lead action level is not health based – putting a level (magnitude) of exposure into a health-based interpretation will both assist

with communication and prioritization of actions. Given this, a final approach that is articulated to these stakeholders should:

  - Describe how an exceedance is communicated in a manner that considers how lead exposure is ubiquitous, and that individuals are exposed from a variety of sources.
    - For example, approximately 20% of children under 7 years of age are consuming at least 5 µg/day of lead through the diet. Put into a drinking water context - for a 5-year old child, that consumes 0.2 L of water per day, that is equivalent to drinking water with a lead concentration of 25 µg/L.
    - IMPLICATIONS: Characterize with greater detail the true adverse effect that the standard is being developed to prevent, and the relationship to how a drinking water "exceedance" should be interpreted.
  - Describe the timeline of necessary actions to reduce lead levels below a certain measured value.
    - Having an understanding of this in terms of implementation is important. For example, assuming that a water supply (or tap) is tested on a regular basis, and that the public (or an individual) is notified in a timely manner, the opportunity for chronic long-term exposure to elevated levels of lead will be greatly reduced. Thus, the exposure is more like that of an acute or sub-chronic exposure. One approach may be to develop guidance that is consistent with US EPA Office of Water values that are developed for specific exposure durations (e.g., 1 day, 10 days, longer-term, and lifetime). These durations are representative of both emergency contamination situations and the reality of some current lead measurements. The guidance should be designed in a manner to determine unreasonable risks to health under the provisions of the Safe Drinking Water Act.
    - IMPLICATIONS: Characterize the health effects of acute, subchronic, and chronic durations of exposure.

- The final approach should be presented in a manner that provides PWS, local officials, and the public with translated and easy to use tools to assist in the interpretation of elevations. Any revisions should be performed in a manner that will provide clear recommendations on the health-based regulation of lead in water.
  - Another approach may be to develop specific guidance for exceedances at schools. In this guidance, individuals would be assumed to consume only half of the total water consumed at schools. For example, elevations of water lead levels at specific taps often presents very specific exposure scenarios, and very personal questions (i.e., "my child only drinks from a fountain outside of the gymnasium two times per week, is that dangerous?"). Knowing this, an approach that describes how a fraction of the total daily consumption of water (~0.15L), might compare to an estimate derived from consuming all water (~ 0.600L) from one source might be useful.

  - A hypothetical "heat-map" style approach, using an approximation of the model-based estimates from the EPA approach is shown in the attached Table 1. Note – this table is hypothetical and a stylized representation that should not be interpreted quantitatively.

- The approaches could be improved by a detailed analysis of the contribution of environmental media to elevated BLLs. This type of assessment is needed to consider
  - The previously described CLPPP data or the Adult Blood Lead Epidemiology and Surveillance program data could be more fully explored for this purpose. For example, EPA should explore these sources of data to inform model parameters (and estimates) describing the contribution of all sources to measured levels of blood lead.
    - For example, a rigorous exploration of clinical outcomes and home lead inspections (of children with blood lead levels over time) may better inform to what extent elevated drinking water concentrations are associated with increased or elevated BLLs.
  - The presented approaches could also be improved by considering how drinking a typical level of water, over various estimates of environmental lead exposure, may change a blood lead level. The change in blood lead levels (ΔBLL; % of increase versus a 0.0 ppb water lead level) over various estimates of total lead uptake could then be considered.
  - This approach would better approximate children with known risk factors, such as minority race/ethnicity; urban residence; residing in housing built before the 1950's; and low family income/poor nutrition.
  - A hypothetical "heat-map" style approach showing how a consideration of measured BLL versus ΔBLL, using estimates from Table 1 (a) [exposures to formula-fed infants] is shown in Tables 2 and 3, respectively. Note – Tables 2 and 3 are hypothetical and stylized representations and should not be interpreted quantitatively. The visualization is presented to show how a determination of "effect" (predicted BLL vs. ΔBLL) is critical, especially as it relates to differences in lead uptake.

Table 1. A hypothetical "Heat-Map" approach to communicating the risk of elevated blood lead levels (EBLLs) from the chronic consumption of various amounts of water over a continuum of water lead concentrations.

(a) Predicted blood lead levels (µg/dL) for **0-6 month old infants** drinking various amounts of water containing 1-45 µg/L of lead.

	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	***20%***	***38%***	***57%***	***76%***	***100%***	***114%***	***133%***	***152%***	***171%***	***190%***	***209%***	***300%***
Water Lead Concentration (µg/L)	1	1.8	1.8	1.9	2.0	2.0	2.1	2.1	2.2	2.2	2.3	2.3	2.6
	4	2.0	2.2	2.4	2.6	2.9	3.0	3.2	3.4	3.7	3.9	4.1	5.1
	5	2.0	2.3	2.5	2.8	3.1	3.3	3.6	3.9	4.1	4.4	4.7	5.9
	10	2.3	2.8	3.3	3.9	4.5	4.9	5.4	6.0	6.5	7.0	7.5	9.9
	15	2.6	3.3	4.1	4.9	5.9	6.5	7.3	8.0	8.8	9.5	10.3	13.8
	16	2.6	3.4	4.3	5.1	6.2	6.8	7.6	8.4	9.2	10.0	10.8	14.5
	20	2.9	3.9	4.9	6.0	7.3	8.0	9.0	10.0	11.0	12.0	13.0	17.5
	25	3.2	4.4	5.7	7.0	8.6	9.5	10.8	12.0	13.2	14.4	15.6	21.0
	30	3.4	4.9	6.5	8.0	9.9	11.0	12.5	13.9	15.3	16.7	18.1	24.3
	35	3.7	5.4	7.3	9.0	11.2	12.5	14.2	15.8	17.4	19.0	20.5	27.5
	40	4.0	6.0	8.0	10.0	12.5	13.9	15.8	17.6	19.4	21.2	22.9	30.6
	45	4.3	6.5	8.8	11.0	13.8	15.3	17.4	19.4	21.4	23.3	25.2	33.4

(b) Predicted blood lead levels (µg/dL) for **1-2 year old children** drinking various amounts of water containing 1-45 µg/L of lead.

	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	***20%***	***38%***	***57%***	***76%***	***100%***	***114%***	***133%***	***152%***	***171%***	***190%***	***209%***	***300%***
Water Lead Concentration (µg/L)	1	2.2	2.3	2.3	2.4	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.9
	4	2.4	2.5	2.7	2.9	3.1	3.2	3.4	3.6	3.8	3.9	4.1	4.9
	5	2.4	2.6	2.8	3.1	3.3	3.5	3.7	3.9	4.2	4.4	4.6	5.6
	10	2.6	3.1	3.5	3.9	4.5	4.8	5.2	5.7	6.1	6.5	7.0	9.0
	15	2.9	3.5	4.2	4.8	5.6	6.1	6.7	7.4	8.0	8.7	9.3	12.3
	16	2.9	3.6	4.3	5.0	5.8	6.4	7.0	7.7	8.4	9.1	9.7	12.9
	20	3.1	3.9	4.8	5.7	6.7	7.4	8.2	9.1	9.9	10.7	11.6	15.5
	25	3.3	4.4	5.5	6.5	7.9	8.7	9.7	10.7	11.8	12.8	13.8	18.6
	30	3.6	4.8	6.1	7.4	9.0	9.9	11.2	12.4	13.6	14.8	16.0	21.6
	35	3.8	5.2	6.7	8.2	10.1	11.2	12.6	14.0	15.4	16.8	18.2	24.6
	40	4.0	5.7	7.4	9.1	11.2	12.4	14.0	15.6	17.2	18.8	20.3	27.5
	45	4.3	6.1	8.0	9.9	12.3	13.6	15.4	17.2	19.0	20.7	22.4	30.3

(c) Predicted blood lead levels (µg/dL) for **2-6 year old children** drinking various amounts of water containing 1 - 45 µg/L of lead.

Water Lead Concentration (µg/L)	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	***20%***	***38%***	***57%***	***76%***	***100%***	***114%***	***133%***	***152%***	***171%***	***190%***	***209%***	***300%***
	1	2.2	2.2	2.2	2.3	2.3	2.3	2.4	2.4	2.4	2.4	2.5	2.6
	4	2.3	2.4	2.5	2.6	2.8	2.9	3.0	3.2	3.3	3.4	3.6	4.2
	5	2.3	2.4	2.6	2.8	3.0	3.1	3.3	3.4	3.6	3.8	3.9	4.7
	10	2.5	2.8	3.1	3.4	3.8	4.1	4.4	4.7	5.1	5.4	5.7	7.3
	15	2.6	3.1	3.6	4.1	4.7	5.1	5.5	6.0	6.5	7.0	7.5	9.8
	16	2.7	3.2	3.7	4.2	4.9	5.3	5.8	6.3	6.8	7.3	7.8	10.3
	20	2.8	3.4	4.1	4.7	5.6	6.0	6.7	7.3	8.0	8.6	9.2	12.2
	25	3.0	3.8	4.6	5.4	6.4	7.0	7.8	8.6	9.4	10.2	10.9	14.6
	30	3.2	4.1	5.1	6.0	7.2	8.0	8.9	9.9	10.8	11.7	12.7	17.0
	35	3.3	4.4	5.5	6.7	8.1	8.9	10.0	11.1	12.2	13.3	14.3	19.4
	40	3.5	4.7	6.0	7.3	8.9	9.9	11.1	12.3	13.6	14.8	16.0	21.7
	45	3.7	5.1	6.5	8.0	9.7	10.8	12.2	13.6	14.9	16.3	17.6	23.9

Notes

1 The predicted blood levels are shown in the cells shaded green (< 3.75), yellow (>3.75 - 5), orange (>5 - 10), or red (>10) and are reported in µg/dL.

2 Lead uptake (µg/day) was converted to blood lead levels (µg/dL) using coeffficients from a polynomial regression model* derived directly from IEUBK (see polynomial regression coefficients described by Zartarian, et al., 2017 and listed below).

3 In addition to uptake of lead from water, the estimate assumes that:

- 0-6 month old infant will uptake 3.19 µg of lead per day from diet, soil, and dust.
- 1-2 year old child will uptake 4.92 µg of lead per day from diet, soil, and dust.
- 2-6 year old child is exposed to 6.38 µg of lead per day from diet, soil, and dust.

* Blood Pb (µg/dl) = $\beta 0 + \beta 1$ (uptake) + $\beta 2$ (uptake)^2 + $\beta 3$ (uptake)^3 (see polynomial regression coefficients described by Zartarian, et al., 2017 and listed below).

Age Category	Bo	B1	B2	B3
0 - 6 months	0.00786	0.547	-0.0013076	6.00E-06
1-2 year olds	-0.00031	0.447	-0.0006372	1.50E-06
2-6 year olds	0.0008612	0.3342000	-0.0003293	5.20E-07

Table 2. A hypothetical "heat-map" approach to presenting predicted blood lead levels (µg/dL) for 0-6-month old bottle-fed infants, over various estimates of total lead exposure (uptake). Table 2 is based on Table 1(a) estimates of typical water consumption (.526L) by bottle fed infants (i.e., the 100% column in Table 1(a)).

Water Lead Concentration (µg/L) \ Total Lead Uptake (µg/day)	3.19	4	6	8	10	12	14	16	18	20	21	22
0	1.7	2.2	3.2	4.3	5.3	6.4	7.4	8.4	9.4	10.4	10.9	11.4
1	2.0	2.5	3.5	4.6	5.6	6.7	7.7	8.7	9.7	10.7	11.2	11.7
2	2.3	2.7	3.8	4.9	5.9	6.9	7.9	9.0	10.0	10.9	11.4	11.9
3	2.6	3.0	4.1	5.1	6.2	7.2	8.2	9.2	10.2	11.2	11.7	12.2
4	2.9	3.3	4.4	5.4	6.4	7.5	8.5	9.5	10.5	11.5	11.9	12.4
5	3.1	3.6	4.6	5.7	6.7	7.7	8.7	9.7	10.7	11.7	12.2	12.7
6	3.4	3.9	4.9	5.9	7.0	8.0	9.0	10.0	11.0	12.0	12.5	12.9
7	3.7	4.1	5.2	6.2	7.2	8.3	9.3	10.3	11.3	12.2	12.7	13.2
8	4.0	4.4	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5	13.0	13.4
9	4.3	4.7	5.7	6.8	7.8	8.8	9.8	10.8	11.8	12.7	13.2	13.7
10	4.5	5.0	6.0	7.0	8.1	9.1	10.1	11.0	12.0	13.0	13.5	13.9
11	4.8	5.2	6.3	7.3	8.3	9.3	10.3	11.3	12.3	13.2	13.7	14.2
12	5.1	5.5	6.5	7.6	8.6	9.6	10.6	11.6	12.5	13.5	14.0	14.4
13	5.4	5.8	6.8	7.8	8.8	9.8	10.8	11.8	12.8	13.7	14.2	14.7
14	5.6	6.1	7.1	8.1	9.1	10.1	11.1	12.1	13.0	14.0	14.5	14.9
15	5.9	6.3	7.4	8.4	9.4	10.4	11.4	12.3	13.3	14.2	14.7	15.2
16	6.2	6.6	7.6	8.6	9.6	10.6	11.6	12.6	13.5	14.5	15.0	15.4
17	6.5	6.9	7.9	8.9	9.9	10.9	11.9	12.8	13.8	14.7	15.2	15.7
18	6.7	7.1	8.2	9.2	10.2	11.1	12.1	13.1	14.0	15.0	15.5	15.9
19	7.0	7.4	8.4	9.4	10.4	11.4	12.4	13.3	14.3	15.2	15.7	16.2
20	7.3	7.7	8.7	9.7	10.7	11.7	12.6	13.6	14.5	15.5	16.0	16.4

Table 3. Predicted change (Δ) in BLLs (%) for 0-6-month old infants shown in Table 2. The shading is not health-based and is presented as a visualization tool to contrast the difference between a BLL evaluation (Table 2) and the ΔBLL evaluation here (shading key: green <10; yellow 10-20; orange 20-50, and red >50).

Water Lead Concentration (µg/L) \ Total Lead Uptake (µg/day)	3.19	4	6	8	10	12	14	16	18	20	21	22
0	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1	16%	13%	9%	6%	5%	4%	4%	3%	3%	2%	2%	2%
2	32%	26%	17%	13%	10%	8%	7%	6%	6%	5%	5%	5%
3	49%	39%	26%	19%	15%	13%	11%	9%	8%	7%	7%	7%
4	65%	52%	34%	26%	20%	17%	14%	13%	11%	10%	9%	9%
5	81%	64%	43%	32%	25%	21%	18%	16%	14%	12%	12%	11%
6	97%	77%	51%	38%	30%	25%	22%	19%	17%	15%	14%	13%
7	113%	90%	60%	45%	36%	29%	25%	22%	19%	17%	16%	16%
8	129%	103%	68%	51%	41%	34%	29%	25%	22%	20%	19%	18%
9	145%	115%	77%	57%	46%	38%	32%	28%	25%	22%	21%	20%
10	161%	128%	85%	64%	51%	42%	36%	31%	28%	25%	23%	22%
11	177%	141%	93%	70%	56%	46%	39%	34%	30%	27%	26%	24%
12	192%	153%	102%	76%	61%	50%	43%	37%	33%	29%	28%	27%
13	208%	166%	110%	82%	65%	54%	46%	40%	36%	32%	30%	29%
14	224%	178%	118%	88%	70%	58%	50%	43%	38%	34%	33%	31%
15	240%	191%	127%	95%	75%	62%	53%	46%	41%	37%	35%	33%
16	255%	203%	135%	101%	80%	67%	57%	49%	44%	39%	37%	35%
17	271%	216%	143%	107%	85%	71%	60%	52%	46%	41%	39%	37%
18	286%	228%	152%	113%	90%	75%	64%	55%	49%	44%	42%	40%
19	302%	241%	160%	119%	95%	79%	67%	58%	52%	46%	44%	42%
20	317%	253%	168%	125%	100%	83%	71%	61%	54%	49%	46%	44%

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COMMENTS SUBMITTED BY

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External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

EPA has spent a good deal of time evaluating life stages for exposure over the last decade or more. The Agency developed a much more nuanced approach with many more categories than the three given here. However, for the purposes of this work, it would seem that the lifestages here are reasonable. The authors must make a strong argument for choosing these collapsed life stages over those proposed by the Agency in the past. Nevertheless, there will be argument from other parts of the Agency suggesting alternatives to the selected life stages. These arguments are likely mitigated, however, by the selection of exposure factors that vary only weakly with age. See discussion below.

<u>0-6 Months Life Stage</u>

In this age category, scenarios are evaluated based on use of infant formula, formulated using tap water, as supplementation during breast-feeding, or in exclusive use. Exposures within this age group are dominated by this formula/tap water intake. Children at this age are less mobile than at later stages and are unlikely to experience significant non-tap water exposures. One may argue that breastmilk exposures may be substantial as well. Some work carried out in the early 1990s (Hu, et al.) suggested that breast milk may also contribute to lead exposures as lead is mobilized from bone stores in pregnant and lactating women. However, presupposing breastmilk contributions with no higher concentrations than those found in drinking water would mitigate any exposures to being comparable; intake of breastmilk with lead levels equivalent to tap water would be supplemented by tap water/formula at essentially the same level. If breastmilk levels were lower, then exposure overall would be decreased.

<u>1-2 Years Life Stage</u>

By age six month, infants are beginning to make the transition to exploring the world and by 1 year they are fully into this process. Through the age of 2 years, mouthing and other similar activities pay an important role in the young child's exploration of her or his surroundings. Locomotion is often accomplished by crawling activities early in this life stage and by walking later. However, in both cases, the child is still close to ground levels and likely to experience more contact with house dust, primarily, and soil later, as outdoor exploration begins. Dust and soil intake becomes a contributor- at some points the major one- in this life stage. One may reasonably argue about the boundaries of this life stage. Should it be 9 months and 3 years, for example. Again, this is a choice that needs to be made. There is support for the 1-2-year life stage that is justifiable. I do not believe that an alternative selection would be any more defensible- just different. I cannot argue persuasively for this particular parsing of life stage, nor can I argue persuasively for any other specific parsing.

0-7 Years Life Stage

I have the most difficulty with this "life stage" as it encompasses a very broad span in maturity. The authors already believe that 0-6 month differs from 1-2 years as evinced by the separation of those two time periods. Now we see an expansion throughout both these ranges and on through childhood. Exposures differ substantially over this life stage and the parameters needed to model this diverse-activity stage vary widely. For Approaches 1 and 2, a measure of central tendency is used, but exposures are likely diverse across the range. In fact, the authors show this and use a weighted average of age-specific values to develop a single parameter for this life stage. On the positive side, however, the point of this life stage is to evaluate cumulative exposure (in the dictionary sense, not the FQPA 1996 sense) experienced by the child that may influence long-term effects such as neurodevelopment, which extends over much of this range, social development, and psychological development, which includes this life stage range and far beyond. Exposures and effects are likely highly variable. Because of this, stochastic simulation approaches such as SHEDS may offer a better evaluation of the impact of exposures on this life stage versus the shorter-duration early life stages.

Other Life Stages

Once children enter school, social development comes into play to affect exposures. This continues onward to older ages, e.g., early and later adolescents and the reduction of soil and dust based exposure and perhaps the beginning of occupational exposure and long-term effects such as hypertension. Further, effects may be gender-specific as children age through early childhood to pre-pubescence and adolescence. There is little evidence for gender-specific lead-based exposure early on, but one may be inclined to examine this as well.

After discussions with my colleagues at the meeting I am more concerned with the lifestages selection. I maintain my acceptance of the 0-6-month lifestages as being important, but also see the need for understanding more about in utero exposures. This is, of course, dependent on the mother's exposure, which I believe should be an important consideration in the modeling work. Models should be developed to relate the drinking water intake of the mother with fetal uptake. This may be most important in the first trimester and during other specific time periods during gestation when the neurological system is under development. After birth, the 0-6-month period is most critical in this regard. The breastmilk/formula period is most important in this regard, and would be effectively covered by the 0-6-month scenario. However, the 6-18-month period is still one of rapid change in the neurological system, which is likely still quite affected by intake of lead and other lead-based exposures. EPA should evaluate alternative modeling strategies during these critical time periods.

An additional discussion focused on the 0-7 lifestage. While many comments were similar to mine given above, there was additional discussion of the 4-5, or 4-6-year age group. My thoughts would be to split the 0-7 age group into 0-4, and 5-7 to account for expected differences in likely routes and pathways of exposure consistent with change in social and developmental stages.

Scenarios

Drinking-Water Only- Since the main focus of the modeling effort is the assessment of a new drinking water standard, is worth the effort to evaluate the incremental effect of drinking water above and beyond the effects of other exposures. Further, it is also important to see the overall effect of all aggregate exposure (now in the FQPA 1996 sense) to lead to determine the impact of drinking water on overall effect. For

example, if drinking water totally dominates exposure, and thus effect, evaluation of other exposures is not warranted. If the converse is true, then the effect of modifying a drinking water standard would be negligible and would incur a cost not warranted by the benefit. Hence one must evaluate both of these scenarios.

The two BLL scenarios are warranted. The current "level of concern" for BLL is 5 µg/dL, hence that is a good modeling baseline. The analysis of the probability of exceeding this standard given a specific value for the drinking water standard is an appropriate value. Further, if a new standard were adopted, say 3.5 µg/dL, it is important to understand water-concentration impact on that standard. Should a new standard be adopted by CDC for BLL, 3.5 µg/dL is as likely as any other, given that current thought is that effects are likely to be observed at levels down to zero. But 3.5 µg/dL is probably about what one can hope for as a reasonable standard. Given these observations, the modeling parameters seem appropriate. One may argue for other standards, e.g., say 2.5 µg/dL or even 1.0 µg/dL, but the feasibility of getting either of these values at the 5%, 2.5%, or 1% level is fraught with difficulty. From a public health perspective, I would like to see a 1.0 µg/dL at the 95% level implemented, but is this really feasible currently? Probably not.

My thoughts were not substantially modified during our discussions. There was a good deal of discussion back and forth on the Drinking-Water Only Scenario. I believed prior to the meeting, and I was not dissuaded by the discussion, that this is useful for the development of the models for drinking-water standards. In my opinion, the utility of a modeling system that could explore the incremental effect brought on by drinking water alone is an important consideration and should be maintained.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

I have some concerns about the model input data. My most serious concern is the lack of variability for dust and soil ingestion across age groups. I am fine with the 0-6-month age group having no soil/dust ingestion as their mobility is very limited. But the lack of variability in non-dietary intake is of concern for the older age groups. Why does it only vary by a few mg (out of 30 or so) across the 6-month to 7 year ages? Dietary lead is similarly fixed across age groups.

Exhibit 6- Drinking Water GSD. What do these numbers represent? The values- 0.0025, etc., do not have any correspondence with what is in the rest of the table. Please clarify.

I reiterate - this must be fixed. This non-physical situation is a glaring error and must be addressed. Others mentioned this in pre-meeting comments and it was mentioned in brief discussion. It is not the most important part of our discussion, but is absolutely in need of modification.

I think the selection of values, how they vary from the IEUBK default values, which is non-systematic, and my sense of reduced variability across life stages bears some discussion by the group. While a consensus is not needed in this type of review, I would like to hear arguments for and against the values selected.

The discussion in the previous paragraph begs for an analysis of sensitivity in the model to variability in these parameters. I still find the fixed or minimally-varying parameters of concern. EPA should check all of these values again and certify that the best measures are being used and assess likely variability in intake parameters that may be seen in a reasonable population.

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

The approaches attempt to address three different issues. Approach 1 looks at the likely distribution of an individual child's BLL and assesses whether a given drinking water standard will increase the probability of the child's BLL above a standard to produce an elevated BLL (EBLL) defined as 5 µg/dL, or ostensibly, any other chosen cutoff. Approach 2 looks at what level of drinking water lead would result in an increase of the expected value, i.e., the mean or geometric mean, BLL for a specific child might be moved by 0.5 or 1.0 µg/dL. These are different things. Approach 1 examines the effect of a given standard on the tail of the distribution of a child's likely exposure while Approach 2 attempts to understand the effect on the central tendency- the expected value- of the child's BLL. Approach 3 differs from the deterministic calculations outlined in Approaches 1 and 2, and looks at distributions across the national population using a simulation approach drawing upon large time-activity databases, and other parameters with variability. It then examines the impact of a specific standard- and its intrinsic uncertainty- and various population parameters, e.g., media, 75^{th} %, 90^{th} %, etc.

The three Approaches are not directly comparable as they are designed to do different things and give different information. Approaches 1 and 2 can be discussed together as they both use the deterministic IEUBK model to investigate the BLL of a specific "representative child." But, again, they are different and address different questions. The probabilistic measures given in Approaches 1 and 2 stem from assessing a geometric mean and geometric standard deviation for a "representative child" then evaluating aspects of a lognormal distribution assuming these parameters. This is a reasonable approach, albeit one that is best thought of in a deterministic fashion rather than in a distributional fashion. One takes values from the literature regarding geometric means and geometric standard deviations, assumes an analytical form for the probability distribution, and calculates the values in question. Approach 1 then evaluates the probability of this lognormal distribution exceeding a specific value, nominally 5.0 µg/dL, but it really could be any test value. This value is completely determined by the geometric mean and geometric standard deviation determined from the input parameters gathered from the literature. In the same way, Approach 2 analyzes the distribution in a different way by assessing how large the drinking water standard would be so as to

affect the central tendency estimate by a certain amount, namely 0.5 µg/dL or 1.0 µg/dL. While doubtless accomplished in separate analyses, in principle, there is no reason both could not be done in the same modeling run by stepping through various drinking water standards then picking out the information needed from whichever one gave results of interest.

Approach 3 is entirely different. It's using an intrinsically distributional approach by creating a large number of simulated individuals and observes the distribution of their BLLs. Input parameters are drawn from empirical time-activity profiles, physiological parameters, home characteristics, etc., to develop the distributions. It then takes these results and looks at percentiles of the distribution of likely BLLs for the entire population thereby examining the impact of a specific lead drinking water standard on the population distribution; SHEDS is a complicated program that requires a large amount of empirical data.

As someone who has done a lot of simulation work in the past, I, of course, prefer the SHEDS approach to the deterministic approach of different implementations of the IEUBL stand alone. But all three approaches give information that is useful to the regulator. No single result is definitive; the three together are much stronger than the sum of the parts.

Despite some comments by others that one, or the other of these approaches is better, I maintain my assessment that the three approaches offer complementary information and are all useful. My colleagues have persuaded me that Approach 3 is indeed the strongest of these Approaches, not that I needed much persuasion. However, Approach 3 is also the most difficult to implement, and the most time-consuming. Further, it requires either substantially more data, which may be site-specific, or a series of assumptions that may, or may not, be appropriate in a given instance. But I do maintain that unique information is obtained from each of the Approaches and that EPA should consider all three in its search for the best information.

b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

The IEUBK is a well-developed and stable model of lead uptake in the human system. It produces estimate of the BLL estimates based on input parameters; it is deterministic. However, it contains a number of default assumptions including distribution among the various compartments of the body, that may not apply under specific circumstances, or, more importantly in the context of this modeling exercise, for different life stages. Further, it calculates a geometric mean and geometric standard deviation, then assumes a lognormal distribution based on those parameters. This results in reduced flexibility in the model. Why lognormal and not, say, gamma-distributed? Finally, the model was developed some 20 years ago; there may be updates of some of the parameters and perhaps a better understanding of the distributional characteristics of BLLs associated with the parameter inputs. This being said, to my knowledge, there is no better deterministic model out there for estimating BLLs than the IEUBK.

I maintain that the IEUBK is getting long in the tooth and may be in need of some reworking, especially in the biokinetic modeling. Advances over the last 20 years have been more than incremental and it may be incumbent upon EPA at this point to develop a new modeling systems, based on newer information about the adsorption, distribution, metabolism, and excretion of lead in the body. A fresh look, perhaps using different input/kinetic parameters and modification of assumptions could be in order.

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

The IEUBK-SHEDS approach tries to overcome some of the difficulties discussed above by using empirical distributions for any number of parameters and implementing an approach that affords a better estimate of population, rather than individual, variability. It also has the ability to produce percentile estimates for the population rather than deterministic estimates for an individual. Finally, IUEBK-SHEDS can be used to account for parameter uncertainty and its impact on the estimates. The deterministic approaches of IEUBK afford estimates of the percentiles for an individual, but does not have the capability of assessing uncertainty in the percentile estimates unless some type of brute-force variation in parameters coupled with sensitivity analyses are brought to bear.

Much of our discussion focused on the use of the IEUBK-SHEDS Approach, Approach 3, in this review. My colleagues were persuasive in their arguments that this was the Approach most likely to yield the best modeling system for assessing lead in drinking water. While Approaches 1 and 2 can yield both deterministic and distributional characteristics for exposures, they do the latter in an artificial manner by assigning a fixed distribution type, i.e., lognormal, to the exposures likely experienced. Further, the change from the mean as a measure of central tendency to the median is problematic as the IEUBK Model assumes the former and the biokinetic parameters are developed accordingly. Approach 3 offers a better mechanism for assessment but at a cost, as discussed above: increased complexity and the need for more input information of additional assumptions. I came to the meeting believing that Approach 3 was the best Approach, but the others offer additional information. I came away with essentially the same thought, although I am more convinced now of the superior nature of SHEDS-IEUBK Approach. Nevertheless, I encourage EPA to continue evaluation of all three Approaches. I may be in the minority in this view as I believe my colleagues may be more attuned to an exclusive use of Approach 3, although I may be misinterpreting some of their arguments.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

I should think that the best approach in all three cases is to validate the models against existing data. This can best be accomplished by using BLL data and any other characterizing data to validate the IEUBK model. For example, one could take a relatively large sample of individuals with measured BLL and collect data on external parameters thought to influence such. This would include drinking water concentration, activity profiles, housing characteristics, etc. I assume that this is how the IEUBKmodel was validated initially.

Given a large enough database, after completing that task, one could match external characteristics of individuals with one another, save the single characteristic under investigation. As an example, consider

drinking water concentration. As a subset of those measured, match individuals according to housing characteristics and other measures such as dust and soil concentrations. Then categorize them by drinking water concentration. One then would essentially have "controlled" for all of the other characteristics and could examine the effect of drinking water concentration on BLL.

Alternatively, one could take such data and implement a statistical rather than heuristic, approach through, for example, a regression model of the type:

$$BLL_j = \sum_i \beta_i X_i + \beta_{DW} DW_j + \varepsilon_j$$

where BLLj is the observed BLL for the jth individual, Xi are the characteristics other than the drinking water concentration that one wants to "control" for that individual and DW_i is the drinking water concentration for that individual. The β_i are the effective contributions of the exposure factors to BLL_j and β_{DW} s the drinking water contribution to BLL_j. The ε_i represent individual-specific errors in the regression model. One could then evaluate the marginal effect of a change in drinking water concentration would have on BLL.

Sensitivity analyses using IEUBK or SHEDS-IEUBK is most easily effected by using a variation of parameters approach to evaluate uncertainty. Distributional characteristics for the population are already built into the system. Alternative methods may afford a more rapid evaluation of the importance of given factors. For example, a change of 10% in a parameter could be evaluated. If the change in BLL were small, then one could ignore the changes in this parameter for future analyses (See discussion below on factorial design.)

I think there was general agreement among my colleagues that a sensitivity analysis is necessary for all three Approaches. Indeed, Drs. Zartarian and Xue in their presentations and discussion indicated that such was either underway or had been done. I have outlined a few approaches in my pre-meeting comments, and others were addressed in the meeting. EPA staff, I believe, are amenable to continued development along these lines and such development was strongly encouraged by the group. I concur with this suggestion and add my full support to this direction for modification and expansion of this work.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

In this section, I will focus on improving understanding of variability and uncertainty on the modeling approaches. This type of analysis for Approaches 1 and 2 is most easily effected through a brute-force analysis in which the DW concentration is varied and the effect on BLL calculated. Using an approach similar to the regression above, one could fix the non-drinking water parameters and simply step through scenarios for drinking water. For uncertainly, a similar brute -force approach could be implemented by varying the non-drinking water parameters through either a one-at-a-time variability to establish the marginal effect of each characteristic, or a factorial design experiment where all such parameters are varied at the same time in a systematic fashion that would afford an understanding of the coupled effects of the characteristics. Such methods are well established, but tedious, time-consuming, and computational demanding. An alternative is to write out the full model and take derivatives associated with each parameter in question.

One could then do a formal error analyzes and determine analytically which parameters are most important in affecting BLL. Here, one would be relying on the detailed analytical model to be a reasonably complete assessment of the variables and parameters needed to describe the relationship between BLL, DW, and the exposure factors accurately. As with any model, the quality of the information obtained from the model is directly related to the quality of the information used to develop the model; garbage in, garbage out. Fortunately, there is a lot of information extant that can be brought to bear on this problem. Such is the point of this entire report.

My colleagues did not dissuade me from this opinion either nor did they try as this was viewed, I believe universally, as a strategy that is needed and appropriate. In fact, there was strong support for a continued evaluation of the sensitivity of the modeling results to the variation in the parameters in the model. This is especially noteworthy in Approach 3, which has the capability including both variability and uncertainty into the results. It is not clear to me in Approaches 1 and 2 how this might be done in a systematic and mathematically precise manner. In Approach 3, distributional characteristics can be included directly. Further, these distributional characteristics can be separated into population variability and model-parameter and model-specification uncertainty to ascertain where research efforts could indeed produce the most effective use of scientists' time to effect the most useful solution to the problem at hand, namely ascertaining the impact on BLLs in populations under varying drinking water scenarios.

COMMENTS SUBMITTED BY

Kathleen L. Vork, Ph.D.

External Peer Review Meeting of EPA's Draft Report, Proposed Modeling Approaches for a Health-Based Benchmark for Lead in Drinking Water

Comment on Background of Charge:

I believe that the working group reports that system-wide action is triggered by an exceedance of 10% of households exceeding the current standard of 15 ug/L. In addition, the working group report indicates that household action would be triggered when individual households exceed some lead concentration in water above the system-wide standard (currently 15 ug/L).

1. MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Comment:

The work presented in materials provided to the panel members describes three valuable approaches for assessing the role of water concentrations of lead on blood lead levels of infants and young children. These approaches all have merit in screening for potential hazards and informing risk managers and the public. The following comments mainly seek clarity to this effort. To begin, some clarifying objectives for this research goal would help focus comments on the merits of current work and/or how this work could be strengthened.

For example, health implications such as decrements in IQ have been associated with increments in lead drinking water levels (OEHHA PHG 2009). For infants who are exclusively bottle fed with formula reconstituted with tap water, this is expected to be a major source of lead exposure. For this vulnerable population, here are some possible objectives:

Develop approaches that can derive:

1) a level of lead in water used to reconstitute commercial formula that would raise a) the probability of infant blood lead levels changing by, for example, 1% over the first six months of life; b) an infant's blood lead level by, for example, 1 ug/dL over the first six months of life.

2) a change in the level of lead in water used to reconstitute commercial formula that would increase a) the probability of infants' predicted background blood lead levels by, for example, 1% over the first six months of life; b) an infant's predicted background blood lead level by, for example, 1 ug/dL over the first six months of life.

Another vulnerable group is children in their second year of life (ages 1 to 2 years). These children have exposure to other sources of lead and may change the level and form of tap water intake (e.g. less intake from reconstituted calcium-rich formula to tap water with and between meals). These changes could raise their blood lead levels closer to levels of concern. Hence, elevated levels of lead in tap water may result in

exceedances of blood lead level of concern (e.g. 3.5 or 5 ug/dL). For this vulnerable population, here are some possible objectives:

Develop approaches that can derive:

1) a level of lead in tap water that would raise a) the probability blood lead levels changing by, for example, 1% over the second year of life; b) a child's blood lead level by, for example, 1 ug/dL over the second year of life

2) a change in the level of lead in tap water that would increase a) the probability of children's predicted background blood lead levels by, for example, 1% over the second year of life; b) a child's predicted background blood lead level by, for example, 1 ug/dL over the second year of life

3) a level of lead in tap water that would reduce to (e.g. 1-or 5%) the probability that blood lead levels in a similarly exposed population would exceed a level of concern over the second year of life

A third group of vulnerable children are those who are still very young but are now spending more time outdoors and away from home (i.e. ages 2 to 7 years old). These children have exposure to other sources of lead and may change the level and form of water intake (e.g. less intake from household tap water with and between meals). These changes could raise their blood lead levels closer to levels of concern and increase the day-to-day level of exposure. Hence, smaller increases of lead in household tap water may result in exceedances of the blood lead level of concern (e.g. 3.5 or 5 ug/dL). For this vulnerable population, here are some possible objectives:

Develop approaches that can derive:

1) a level of lead in tap water that would raise a) the probability blood lead levels changing by, for example, 1% over ages 2 to 7 years; b) a child's blood lead level by, for example, 1 ug/dL over ages 2 to 7 years

2) a change in the level of lead in tap water that would increase a) the probability of children's predicted background blood lead levels by, for example, 1% over ages 2 to 7 years; b) a child's predicted background blood lead level by, for example, 1 ug/dL over ages 2 to 7 years

3) a level of lead in tap water that would reduce to (e.g. 1-or 5%) the probability that blood lead levels in a similarly exposed population would exceed a level of concern over ages 2 to 7 years

Consider modeling the second 6 months of life for infants. For this age group, similar BLLs to those predicted for the 0 to 6-month age group were predicted by the IEUBK model using default parameter values and set to percent above 5 ug/dL. However, the 0 – 12-month exceedance were slightly less (% above 13.8, 13.4 and 11.2 for the 6 to 12, 0 to 6 and 0 to 12-month groups respectively).

The IEUBK model allows for changes in GSD up to 1.8. However, the combined GSDs of 1.6 for biological and 1.6 for environment variability exceed 1.8 (Exp(sqrt(ln(1.6))^2 + (ln(1.6))^2) = 1.944. There are some sources of variability and uncertainty that may need to be addressed for each age group. For example,

1) Some factors that could influence blood lead predictions for 0 to 6-month infants might be level of "hardness" in the water, calcium in formula and lead in maternal blood.

2) Some additional factors that could influence blood lead predictions for the 1 to 2-year age group might be the history of blood lead in infancy and uptake of lead from food and residential soil and dust.

3) Some additional factors that could influence blood lead predictions for the age 2 to 7-year age group might be the history of blood lead in earlier childhood and uptake of lead from food and nonresidential soil and dust.

2. MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

Comment:

Can rate of breastfeeding among exclusively breast-fed infants be used as a surrogate for formula intake? There is a recent assessment of these rates that might be better than the sparse data (N=7) on rates of formula intake (Arcus-Arth et al 2005).

Arithmetic and geometric means have been selected for various parameters based on whether the data is "highly variable" or "due to the lognormal distribution of the input data". Have the "highly variable" datasets been examined for sources of heterogeneity?

3. MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model.

"Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

Comment:

Each approach has merit and informs risk managers at national, state and local levels. It is clear that efforts at Federal, State and local levels continue to be vital in preserving the public's health. Approach 1 is a useful screening tool at water district and local levels. Approach 2 relates to approaches used, for example, in California to determine the public health goal for lead in drinking water and for other programs at the state

and local level. Approach 3 provides a means 1) to assess the general level of lead exposure from environmental sources across the nation and 2) assess what water concentrations would need to be to help prevent blood lead exceedances at the population level.

Each approach also has limitations and uncertainties. Adjustments for safety and uncertainty would be an important component to incorporate in each approach.

b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

Comment:

The greatest strength of the IEUBK model is its ease of use. The examples in this report of predictive success seem reasonable. However, compared to the IEUBK model, the Leggett model (for example) is completely transparent and changeable. Whereas over half of the IEUBK model parameters are fixed. With an open code model there are more options to explore. For example, children with multiple years of exposure, changes in time averaging can be explored along with other important biological variables such as body weight and hematocrit.

It may be important to explore whether infants and children on the extreme end of factors such as low birth weight, high background lead burden prior to start of exposure period of interest, low hematocrit etc. are covered by a composite GSD.

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

As tap water becomes an increasingly minor contribution to blood lead, model predictions are more difficult to check with measurements because of the "noise" in the data. However, the SHEDS-IEUBK model may best serve a population that experiences a substantial increase in lead levels in tap water. The IEUBK model is easy to use as a screening tool.

4. MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES
Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

Comment:

I defer to others on the panel who are more familiar with conducting sensitivity analyses on complex models. In my limited experience, a targeted sensitivity analysis guided by prior knowledge of sensitive parameters can be an efficient approach.

5. How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

Comment:

I defer to other experts familiar with the superfund program to draw on analogous approaches for assessing site-specific exposures.

- In the California lead in construction standard, where day to day and within day variability in worker exposure can be substantial, pre-emptive protective measures are required for workers assigned to trigger tasks or events. These tasks/events are assumed to result in elevated blood lead levels. Examples of such events may be changes to water systems, water treatment changes and changes in other sources of lead exposure. Then, sample collection during tasks/events designed to obtain a representation of lead in the media of interest (e.g. air in the case of workers and water in the case of household residents) can be obtained and blood lead either modeled or measured can determine whether protective actions are sufficient. In some highly variable exposure conditions, lookup tables or "heat diagrams" have been developed (as described in the June meeting by Dr. Nascarella).

Additional clarifications, limitations and future directions

Add definition of terms for clarity. For example, define historic exposure (exposure leading to an initial blood lead level prior to the exposure time being modeled) versus background exposure (ongoing exposure from non-water sources).

Add a discussion of assumptions and assessment of alternate assumptions. For example, an assumption about background exposure to soil and dust was made for the age group 0 – 6 months. Briefly discuss the impact of a different assumption as suggested in the June meeting. In addition, the IEUBK model is calibrated for childhood exposures. If modeling adult women is added to the present effort, an alternate approach and model would be needed. One recommended analysis would be testing the impact of historic (different intensity and chronicity prior to the exposure time being modeled) on the time-to-decay from unacceptable to some determined lower blood lead level for women of childbearing age.

Approach 3 results change the current assumption of 20% contribution to blood lead from water. This assumption is used, for example, in California for deriving a public health goal (PHG). Approach 3 provides a data-derived percent of lead exposure from water. If the current assumption of 20% contribution was held constant, what would the levels in other sources need to be to keep blood lead levels below 3.5 and 5 ug/dL?

Approaches 1 and 2
With lower levels of lead from widely distributed sources such as ambient air, diet and lead paint- or leaded gas-contaminated soil and dust, lower blood lead levels in the general population would be expected. As a result, more elevated blood lead levels from people exposed to "hot spot" background sources of lead such as contaminated soil from nearby point source emissions, contaminated surfaces in homes and vehicles of lead workers (Hipkins et al 2004, MMWR 1998, 2008) and nearby uncontrolled lead paint removal projects,

may be more detectable from the general population. However, including less frequent but substantially elevated blood lead levels in a regional or national average may mask the effect of those "hot spot" exposures. Hence, more customizable approaches such as 1 and 2 are vital for screening purposes in communities with suspected above average sources of lead exposure or blood lead levels. In addition, saturation kinetics plays a role when frequent spikes followed by very low levels of exposure occur over time. The variability associated with non-national sources and non-constant exposure over time may be greater than the 1.6 GSD currently assigned to exposures in the general population.

Approach 3
Results from approach 3 presented to the panel and in a manuscript accepted for publication in EHP illustrate the impact of lead levels in water systems at and below the current system action level of 15 ppb on keeping blood lead below defined levels in defined age groups. This analysis did not apply a factor representing uncertainty. This is a limitation in the approach as presented.

Uncertainty factors for specific age groups could be informed by conducting a comprehensive stratified uncertainty analyses as suggested by panel members during the June meeting (see remarks made by Prof. Georgopoulos).

Saturation kinetics at very low levels of exposure is subtle and thresholds that indicate a level in which saturation begins in not based on biology (Leggett 1993, OEHHA 2013). Frequent high followed by very low levels of lead exposure changes the kinetics of lead in the human body (Leggett 1993). Recent attempts to limit the frequency as well as intensity of lead intake from contaminated food sources appears (see section 5.2, WHO 2011) in recognition of this effect. Back-calculated water levels leading to specified blood lead levels using the IEUBK model may be higher than a model that incorporates saturation kinetics. This is evident in the effort undertaken in support of updating the worker standard for lead in California (see Table 2 OEHHA 2013). A comparison of back-calculated water levels of lead would be useful to evaluate the impact of frequency and intensity of episodic exposure, predicted blood lead and back-calculated water lead. This comparison is currently a source of uncertainty in the present analysis.

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Arcus-Arth A, Krowech G, Zeise L, (2005) Breast milk and lipid intake distributions for assessing cumulative exposure and risk, Journal of Exposure Analysis and Environmental Epidemiology, 15, 357-365.

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California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2013), Estimating workplace air and worker blood lead concentration using an updated physiologically-based pharmacokinetic (PBPK) model, Vork KL, Carlisle JC, Brown JP. ; Available at https://oehha.ca.gov/air/document/oehha-presentation-pbpk-model-blood-lead-and-worker-exposure

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Appendix I

REVIEWER POST-MEETING COMMENTS ORGANIZED BY CHARGE QUESTION[1]

[1] This appendix provides post-meeting comments organized by charge question for the seven reviewers (all except Dr. Prévost) who provided written comments to ERG after the meeting.

1.0 COMMENTS ORGANIZED BY CHARGE QUESTION

This report provides post-meeting comments, organized by charge question, for the seven reviewers who provided post-meeting comments. The eighth reviewer, Dr. Prévost, did not provide them.

1.1 MODEL SCENARIOS

Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA. Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 ug/dL and 5 ug/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Reviewer	Comments
Georgopoulos	The selection of the three life stages (0-6 months, 1-2 years, and 0-7 years) for the modeling analysis represents a reasonable compromise given the limitations in available data and in the formulation of the models (particularly IEUBK) that were used. Increasing the temporal resolution of the life stages modeled would in principle be feasible (though not straightforward) via the incorporation of available physiological and exposure factor information (of course, the latter would still have substantial data gaps). However, it does not appear that corresponding clinical and epidemiological data are available at such resolution to justify the effort required by a more "temporally refined" analysis. It would be very useful however to "break" the 0-7 years life stage in a way that would differentiate pre-school and school years (as the exposure patterns of the child change substantially with its introduction in the school environment). Future studies (that would require development and application of a "next generation" IEUBK-type extended model) should consider explicitly *in utero* exposures (that may be critically important for neurodevelopmental effects) by incorporating the appropriate life stages for both the mother and the fetus (in a combined mother-fetus PBPK model formulation). Since this option is not currently available, this recommendation is relevant not only to life stage selection but to modeling needs that should be eventually addressed. At this point it should be reminded that IEUBK has been formulated and applied as a model appropriate for considering exposures representative of each year of the child's life and not for considering relatively short-term and transient exposures. In the past, the standard recommendation for applying IEUBK has always been that "exposures must be for ≥1 day/week for 90 consecutive days"; however, the modeling effort under review adopts a 30 day period for its analysis under Approach 3, a matter that needs further explanation and justification (beyond the reference currently provided in the technical document describing the modeling effort under review). Regarding the strengths and weaknesses of the modeling scenarios conducted, these can - and should - only be evaluated specifically in the context of the modeling approaches that employed these scenarios. The strengths and weaknesses of the different modeling approaches are the subject of Question 3 and are discussed in the response to that question (though in this reviewer's opinion, discussion/evaluation of the modeling

Reviewer	Comments
	framework and modeling approaches should logically precede the discussion of the scenarios used). Nevertheless, it should be pointed out here that Approaches 1 and 2 appear to be using the premise that applying IEUBK with input values that represent measures of central tendency (such as the geometric mean) for various exposure-related variables/parameters of the model, would produce corresponding outputs that also represent measures of central tendencies of distributions of these outputs for subpopulations with the aforementioned variabilities in exposure factors. This is not justifiable and requires re-evaluation of the relevance and interpretation of the scenarios employed in Approaches 1 and 2, including those considering water-only exposures, which represent an "extreme" situation (and rather implausible beyond the infant life stage) that is more relevant to a model sensitivity analysis. Approaches 1 and 2 present interesting case studies but in fact they reflect the biokinetic responses to specific exposure scenarios that are not generalizable to the population of concern (all children in the US or even children within a population represented by the NHANES sample considered in the application of Approach 3). On the other hand, Approach 3 employs a probabilistic methodology for assessing aggregate exposures via the SHEDS model; this approach is scientifically sound with respect to exposure characterization (though the coupling with a regression-based equation representing IEUBK outputs requires further discussion) and the scenarios modeled using this approach are relevant to "real world" situations and furthermore conform with current practices for multimedia/multipathway exposure and risk characterization. Though the levels of the two target BLLs considered are appropriate, there is concern as to whether the parameterizations of the models (even for Approach 3) are appropriate for calculations at the upper tail percentiles of the exposure distribution (where lognormality assumptions may not be valid). Though this is not an alternative scenario per se, it might be useful to consider order statistics (or "statistics of extremes") for distributions of the upper tail percentiles of observed BLLs and compare those with upper percentiles resulting from distributional (probabilistic) model calculations. Furthermore, it should further be emphasized that the scenarios involving NHANES (and NHEXAS) populations and corresponding exposure-relevant factors produce as outputs exposure distributions (and corresponding upper percentile estimates) that are strictly relevant to these populations and not to the US population (which includes potentially highly exposed subpopulations as well as sensitive subpopulations that are not "captured" in the NHANES samples). The Approach 3 scenarios that are presented in the document under review were indeed simulated (and found to perform in a satisfactory manner) with inputs that are appropriate and relevant for the populations considered. It would be very informative to consider and perform scenarios that consider inputs not limited to those relevant to the NHANES (or NHEXAS) populations but instead use inputs (e.g., water consumption rates from US EPA's Exposure Factor Handbook) that apply to the distributions of the overall US population and compare the output distributions (not only central tendency measures and selected upper percentiles) with those derived for the

<table>
<tr><th>Reviewer</th><th>Comments</th></tr>
<tr><td></td><td>NHANES population (using NHANES water consumption rates). It would also be very informative to run selected scenarios for the populations of different climate/ physiographic regions of the US and compare the effect of different exposure factors (as different climate/physiographic regions, such as e.g. the northeast vs the southwest, also have different soil properties, housing characteristics, indoor/outdoor activity patterns, etc.).</td></tr>
<tr><td>Goodrum</td><td>Please comment on the strengths and weaknesses associated with the decision to model three life stages: 0-6 months, 1-2 years, and 0-7 years. Please comment on whether there are additional life stages that should be considered by EPA.

The selection of the three age groups make sense:

• The 0-7 year age group is a standard age range when running the IEUBK model and provides a benchmark for comparison with other shorter age group periods. A limitation of this averaging time is that the year-to-year variation in BLLs is sufficient to raise concerns that a health-based benchmark that corresponds to 7-year average exposures may not be protective of infants and toddlers, which represent sensitive developmental periods when potentially higher exposures and BLLs may occur.

• The 1-2 year age group is a good choice for a 1-year interval given the relative body-weight normalized water consumption rate is highest (and essentially equal to 2-3 year age group). Something like Table 1 (see next page) would be a helpful addition to the report; otherwise Exhibit 6 gives the impression that the 1-2 year age group is not the period of peak exposure since the water consumption rate is about 2.5-fold lower than that of the 0-1 year age group.

• The 0-6 month age group makes sense from the point of view of accounting for exposures to formula-fed infants. Evaluating exposures associated drinking water specific to formula-fed infants (Report Appendix A) is good, and is consistent with EPA's original recommendations on the use of the IEUBK model (see USEPA 1994a, Section 2.3.3.2). The major uncertainty is that NHANES data are not available from which to estimate baseline BLLs for this age group.

Table 1. Body weight (BW)-normalized water consumption rate by 1-year age groups.

<table>
<tr><th>Age Group[a]</th><th>GM Consumption Rate (L/day)[b]</th><th>Mean BW (kg)[c]</th><th>BW-normalized CR (L/day-kg)</th></tr>
<tr><td>0 to <1</td><td>0.410</td><td>7.2</td><td>0.0570</td></tr>
<tr><td>1 to <2</td><td>0.151</td><td>11.2</td><td>0.0134</td></tr>
<tr><td>2 to <3</td><td>0.176</td><td>13.3</td><td>0.0133</td></tr>
<tr><td>3 to <4</td><td>0.193</td><td>15.5</td><td>0.0124</td></tr>
<tr><td>4 to <5</td><td>0.197</td><td>18.0</td><td>0.0110</td></tr>
</table>
</td></tr>
</table>

Reviewer	Comments

5 to <6	0.213	20.3	0.0105
6 to <7	0.228	22.2	0.0103

[a] The age range is presented inconsistently in the Report, and I recommend using the "<" symbol to clarify which age group is inclusive of the high end of the range. For example, Exhibit 5 is good (e.g., "0 to < 1 Years"), but Exhibit 6 has "0-1 Years" and "1-2 Years", which is ambiguous as to which group a person age 24 months is in.

[b] Based on Exhibit 6 of the report, which relies on NHANES 2005-2011.

[c] Based on Equation B5-f in the IEUBK Technical Support Document, also cited in the Report.

Some panel members recommended that EPA consider a scenario to reflect *in utero* exposure and risk to the fetus – which is of course the focus of the current EPA Adult Lead Model (ALM). I agree that it would be helpful to include a set of scenarios using the ALM model as a "check" on the range of water concentrations (benchmarks) calculated with the IEUBK model scenarios. I'd offer the following recommendations if EPA elects to expand the scope in this manner:

- Run the ALM model in "default input" mode and generate model runs that provide similar risk metrics as the Approaches 1, 2, and 3. That is, report on the delta in BLL at various points in the distribution after adding in a water consumption pathway, and report on the absolute blood leads and probabilities of exceedance of various reference levels.
- Run the ALM model in "updated input" mode, consistent with USEPA's current thoughts about the most up-to-date science on the age range relevant to women of child bearing age, water consumption rate, geometric mean and GSD BLLs.

I do not think additional life stages need to be modeled since the proposed age ranges effectively bracket the developmental periods of concern.

Please also comment on the strengths and weaknesses of the modeling scenarios conducted, i.e., exposure scenarios for drinking water only and all pathways, and target BLLs (3.5 µg/dL and 5 µg/dL at several upper tail percentiles of the population). Please identify additional scenarios that would add utility.

Drinking Water Only

I find it helpful to present results for a Drinking Water (DW) Only scenario, whereby all non-drinking water pathways are set to zero. However, EPA should reconsider the following statement, which is used to describe the rationale for this scenario (Report p. 42):

> "To explore the direct impact of drinking water alone, model runs were also conducted assuming no other sources of lead".

This implies that equal weight is given to the results based on the DW-only scenario, which I suspect will not be the case. It is highly unlikely that the final selection of a health-

Reviewer	Comments
	based benchmark would be based on this scenario, since it is expected that there will be a non-zero baseline BLL across age groups. The main utility of this scenario is to understand the incremental change in the various risk metrics once a baseline scenario is included. So I would recommend revising the rationale to something like: "To explore the impact of adding in a baseline (non-drinking water) contribution to BLL to each of the risk metrics, results are presented both for model runs excluding baseline (i.e., drinking water only) and including baseline." It would be helpful to also run a baseline only scenario – so results would be available for baseline only, drinking water only, and finally – the combination of baseline and drinking water. As noted in my comments below (see Charge Question 3), I believe that baseline can be effectively represented by mining the summary statistics from the NHANES survey datasets, an approach that has already been used in published lead modeling research (Maddaloni et al. 2005). **Blood Lead Reference Values (BLRV) of 3.5 µg/L and 5 µg/L** The choices make sense in the context of a science-policy decision, given recent and ongoing discussions from CDC and its advisory panel, the Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP). However, in this Report, the rationale can be more clearly explained. As written, the clues are there – footnotes 15 and 16 on p. 41 give the 97.5th percentiles for the NHANES datasets for different survey years, and on p. 52, there is a reference to Zartarian et al. 2016, though the description of Approach 3 is very misleading: "Approach 3. Estimate the amount of lead in drinking water that would result in a population's predicted distribution of BLLs having a 95th or 97.5th percentile BLL of 3.5 or 5 µg/dL (Zartarian et al. 2016)" Based just on this statement, the reader is lead to believe (incorrectly) that there is a distribution representative of baseline for which the 95th percentile is 3.5 µg/dL and the 97.5th percentile is 5.0 µg/dL. Later, in the summary of results, it is clear that both percentiles are evaluated for both target BLLs, however, the basis is not at all clear. Additional clues: • Zartarian et al. (2016) state, "CDC is considering changing the reference value to 3.5 µg/dL (ATSDR 2016, p. 17)". • ATSDR (2016, p. 17) states, "CDC is continuing to discuss the possibility of lowering the current BLRV from 5 to 3.5 µg/dL." And also, "The former ACCLPP voted to approve two recommendations to CDC in 2012. First, eliminate and replace the terminology of "blood lead level of concern" (i.e., >10 µg/dL) with a reference value based on the 97.5th percentile of the distribution of BLLs in children 1-5 years of age as measured by NHANES. Second, reevaluate the BLRV every four years. CDC concurred or concurred in principle with ACCLPP's recommendations." From this information, it is clear that the basis for considering both a BLRV of 5.0 µg/dL and 3.5 µg/dL is that the former is the current CDC reference level based on the 97.5th

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	percentile for 1-5 year olds from 2007-2011 NHANES, and the latter is the 97.5th percentile for 1-5 year olds from the more recent 2011-2014 NHANES, and will likely be adopted as a new reference value. My specific recommendations to clarify the rationale are: 1. In Section 2.2 (Overview of Adverse Health Effects Associated with Lead Exposures), specifically in the second paragraph where public health agency perspectives are introduced, expand the text (or add a new paragraph) to talk about blood lead reference values (BLRVs) and CDC's current position. Introduce the term BLRV and use it throughout the report to promote consistency with ACCLPP's recommendations; do not use "target BLL" (as in the charge question above). 2. Introduce the 97.5th percentile summary statistics from NHANES here (you can repeat it again later in the footnotes 15, 16 too). Underscore the important point that an upper percentile of the distribution from NHANES does not denote a threshold effect level below which adverse effects are considered to be negligible; rather, it is a policy decision to establish a high-end BLL reference value that most of the population will not exceed. 3. Introduce the concept of how to interpret the percentile of a probability distribution of BLLs. It conveys the fraction of the population that is expected to have a BLL less than or equal to a specified BLL – this is the usual interpretation from the NHANES summary statistics. It also conveys a probability that an individual selected at random (from a group of similarly exposed individuals) will have a BLL less than or equal to a specified BLL. This is the context for which IEUBK model runs are typically interpreted. A short discussion along these lines will help set the stage later in the Report for how to interpret the model runs relative to the BLRVs.
von Lindern	*Life Stages:* EPA has identified three age sub-groups with the impetus, presumably, to identify and assess potential outcome blood lead levels for the most vulnerable population sub-groups. Blood lead estimates will be developed through application of the IEUBK model for lead for each of the three age groups. Significant health risk will be evaluated by comparison of predicted blood lead levels to threshold health criteria (3.5 µg/dL and 5µg/dL). Several questions arise as to the appropriateness of these categories. It is generally recognized that younger children and fetuses are at greatest risk due to several intersecting factors, generally related to exposure, absorption, and health effects. *Exposure and Intake Considerations:* Primary intake routes change markedly during the fetal to school-age development. Fetal exposure is maternal, largely reflecting the mother's blood lead level exacerbated by mother's nutritional status, diet, bone lead store, and habits (smoking, etc.) An infant's greatest exposure in the first 6 months is believed to be through breast milk, (thought to be reflective of the mother's blood lead status) or formula, the latter prepared by tap water being a central concern. Polluted air and dusts accumulating on surfaces (such as pacifiers) may add incidental increments. Additional exposure sources are introduced in the first year as children transition to

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	solid foods (which may be contaminated), and begin to explore their environment through hand-to-mouth activities (incidentally consuming contaminated dusts in the immediate home environment). Substantial evidence suggests that incidental hand-to-mouth soil and dust intakes peak at 1-2 years until about age 4-5 years, and then decrease to typical adult levels around age 12 years. As toddlers, and then pre-school children, expand their immediate environment, additional soil/dust sources in the home, neighborhood and daycare environs become contributors; the greater community sources become important as children enter school and playtime activities. Drinking water consumption is largely formula-driven for the infant and then increases with age as children mature. *Absorption considerations:* The bioavailability of lead intake also varies by each of these exposure routes (and within each route) due to both the physical and chemical characteristics of the intake media, and the nutritional and behavioral predisposition of the child, which can also be age dependent. Generally, the most useful measure of overall absorption is the blood lead level which is often related directly to adverse outcomes in several organ systems. *Developing Organ System Considerations:* Although numerous organ systems are adversely affected, the most particular concern is Central Nervous System (CNS) irreversible brain and nerve damage resulting in lifelong intelligence deficits and behavioral manifestations. These effects are most severe from conception through pre-school (5-6 years) as the CNS develops. The challenge to EPA is to identify those age categories where exposure, absorption, and developmental factors combine to effect significant risk of unacceptable adverse outcomes. Because there are multiple exposure sources and co-factors with both individual and age-specific variation, more than one group may contain most vulnerable members. It is incumbent on the Agency that any protective measures adopted to mitigate these risks also be protective of all other age groups; and in this case with particular attention to the effects of drinking water exposures. The three age groups proposed are appropriate for the proposed analyses, provided the 0-7-year category is developed by year, and not in aggregate. It is likely that peak effects of drinking water lead exposure to infants occurs in the 0-6-month age period for formula–fed children, and it is advisable to evaluate this group separately. This is the age-group in which drinking water lead would be the primary (and perhaps only source of lead intake). However, it seems likely that drinking water (and associated lead) intake would increase as water replaces formula and total food intake increases as children grow and transition to solid food. This 1-2-year age dietary transition period coincides with peak soil/dust ingestion rates and is an appropriate age group to assess. Total lead intake and blood lead, however, may continue to increase as these children grow, access soil and dusts in the home and increase the dietary and drinking water lead increment. Peak blood lead levels may occur in the 3-4-year age range. This age band should also be evaluated separately, and not in aggregate with other age children in the 0-7-year analyses. Older children and adults would likely be protected by any action taken to mitigate 0-6 month, 1-2, 3-4 and 0-7-year risks, with exception of pregnant women as maternal

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	absorption directly affects the fetus. As a result, potential fetal (or maternal) exposure should also be evaluated. The 1-2, 3-4 and 1-7-year age groups have been extensively characterized and verified in numerous IEUBK model applications by the Agency, depending on the definition of age 0. Including children <1 year would be outside the traditional application of the IEUBK model. Less experience and verification have been accomplished with the 0-6-month old and none with fetal exposure, excepting some Adult Model applications that may be applicable. There is a need for more emphasis on fetal and maternal blood lead levels for nursing mothers with concurrent lead exposure. The uncertainties associated with placental transfer of lead, calcium demand on the mother as the fetal skeleton develops, maternal nutritional and behavioral considerations, and the mother's dietary (especially drinking water) lead intake need to be examined and appropriate margins of safety considered. *Modeling Scenarios:* The Agency's proposed modelling strategy to address these combined exposure and absorption effects and organ exposures and vulnerabilities is somewhat different than the typical approach of identifying the most vulnerable population and then presuming mitigating exposures for that group protects all members of the population. There is confusion associated with EPA's short and long-term assertions that, on one hand, this is a statistical exercise to adapt the IEUBK to fit national databases and is not health-related, versus developing a model to facilitate risk assessment and mitigation programs that will be used to develop quantitative health indices and regulatory action levels. It is difficult to provide meaningful comment on the appropriateness of any modeling exercise without knowing the purpose of the model or how it will be used. The strategy to develop model scenarios that evaluate blood lead increments for drinking water only, and all pathways combined, suggests dual or multiple purposes. From a risk assessment perspective, the water-only scenario seems most applicable to 0-6-month formula-fed children as a most sensitive group, due to the high intake rate of water (actually *dose*, both absolute and relative to other sources). This age group is of particular concern as it may be the most vulnerable to water lead exposure, most susceptible to spikes in exposures, and least understood with respect to modeling blood lead or health effects. EPA should develop the discussion of these uncertainties, conduct appropriate quantitative and qualitative sensitivity analyses, and consider these in the context of approaches by WHO, and other international organizations and countries that have developed health-protective water criteria for infants. It also seems essential for health and risk assessment that older children be evaluated with aggregate exposures, assessing risk relative to the likelihood of exceeding the threshold health criteria. This is because developmental vulnerability, higher co-exposures, and additional exposure co-factors combine to exacerbate intake and absorption in some children with age. The use of IEUBK to assess water-only scenarios for older children suggests the Agency is developing a platform for either assigning relative liability to the various sources, or determining risk increments for children that have minimal exposures and blood lead

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	levels. Having minimal or high exposures in the US today is most often dependent on sources and risk co-factors related to socio-economic advantage or disadvantage. As a result, these potential evaluations raise both risk communication and environmental justice issues, as the IEUBK has been used extensively to allocate responsibility for increased absorption among the sources of lead. The difficulties of making source allocation determinations in those regulatory and litigation schemes are well-known and reflect the shape of the dose-response and health effects curves at lower blood levels. In analyzing the nonlinear absorption and health effects predictions generated in a multi-media exposure scenario, relative contributions can be manipulated by the order in which the sources are introduced into the models. Current consensus is that the first lead introduced at the lowest blood level is absorbed at a higher rate and does more organ damage per unit of absorption. Thus, fetal lead might be expected to result in the highest unit rate of irreversible health damage; and the difference in risk and manifestation of adverse effects between unexposed or advantaged (e.g., middle and upper income, white, post-1970 suburban) mothers and fetuses and the poor living in areas with sub-standard housing and deteriorating infrastructure may be marked. Relative risks to those with even low exposures (e.g., urban, low and middle income, mixed-age housing) may be significant when compared to more affluent communities. Maximum relative risk (and the highest rates of absorption and adverse health effects) due to water alone may well occur in formula-fed infants, as EPA alludes to in the discussion; and the differences in risk and outcome between exposed and minimally-exposed populations might be notable. The most severe adverse health effects, however, are likely associated with the highest blood lead levels due to all sources combined. In these cases, incremental exposures due to any source (i.e., drinking water) introduced to a child with an already high blood lead level will significantly exacerbate overall risk, but at a lower (but nevertheless deleterious) absorption rate. These children are also likely to be among the more disadvantaged due to poverty, housing, and other socio-economic factors. Although EPA does introduce drinking water lead both as the initial source (in the drinking water only scenario) and as an addition to other sources (incremental), it is troublesome that EPA's analysis implies markedly different source attributions than would be indicated with application of IEUBK default parameters (see Model Input discussion below). The results could be interpreted to imply that the most severe drinking water health effects could be expected at lower concentrations in affluent communities, while higher levels could be accommodated in poorer communities already experiencing excess absorption. Although EPA indicates that this is not a health-related analysis, but rather is a statistical exercise to fit observed blood lead distributions, it is difficult to imagine future uses of these models that will not be health-related. In the development of any health benchmark, the eventual risk communication challenges to water purveyors, public health, school and community advocates should be a paramount concern. *Target Blood Lead Levels and Upper Limits of the Blood Lead Distribution:* EPA justifies the "non-health related" purpose of this exercise in the definition of Elevated Blood Lead Levels (EBLLs). For the purposes of this analysis, EBLLs were defined as at or above

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	3.5 µg/dL or 5 µg/dL, and emphasizes that these levels are not based on preventing adverse health outcomes, but rather on a statistical approach considering BLLs at the national level (i.e., the 97.5th percentile BLL based on 2011-2014 and 2007-2011, NHANES data for 1- to 5-year-old children, respectively). Despite the denial that this analysis is health- related, blood lead criteria, effectually, have always represented both a health effects threshold and an upper limit of the contemporaneous national blood lead distribution. This has evolved through a continuing cycle of recognizing adverse effects at contemporaneous levels, effecting policies to reduce overall blood lead levels, observing more deleterious effects at the lower blood lead levels, and initiating additional measures to further lower absorption levels. It was recognized long ago that this trend will continue toward zero blood lead, as there is no safe level of lead. EPA should indicate what health threshold levels the Agency believes are applicable at this time, and whether those differ significantly from the statistical upper limits of the populations evaluated. If these levels are not significantly different, then reviewers are hard-pressed not to consider health implications. EPA's strategy of evaluating drinking water lead levels associated with both mean per unit blood lead increments and 0.5% and 1.0 % changes in the number of children expected to exceed the 3.5µg/dL and 5.0µg/dL blood lead criteria suggests an attempt to accommodate a constellation of potential uses of the results. The document under review alludes to a strategy of assessing the results against a target distribution of 95% and 97.5% of children below these blood lead levels. It is difficult to comment on the appropriateness of these criteria and percentiles without knowing why and how the comparisons will be applied. It is doubly difficult, and would require pages of qualifying statements, to comment on the appropriateness in the context of the IEUBK applications, model inputs, model type employed, and whether the percentage criteria are treated as the proportion of the population meeting that criteria, or the risk that an individual in that population will exceed that criteria. All of these selections must be made in concert with the intended uses of the model.
Loccisano	Life stages: The age groups generally seem appropriate, but there should be more of a break-down with the 0-7 years (i.e., 2-3 years, 4-5 years, etc). The 0-7 years life stage is of particular concern as this is a broad time span. EPA obviously understands that 0-6 months differs from 1-2 years as they have already broken out these time periods, but exposures over this broad time span of 0-7 years will be very different as children are developing rapidly and their behaviors will change. However, this broad time span may be useful for evaluation of cumulative exposure that may influence long-term neurodevelopment. Fetal exposure should also be considered. The IEUBK model is limited in its ability to model this life stage but this should not preclude EPA from doing so. A physiologically-based pharmacokinetic model would allow for examination of maternal, fetal, and infant exposures (from breast milk). A PBPK model could also be extended to allow for modeling of childhood exposures and would allow for incorporation of variability in both exposure and biokinetic parameters.

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	Several studies[1] have reported on delayed puberty in girls being associated with elevated BLLs. This is another endpoint that should be considered in the modeling approaches, so extending the modeling efforts to include this life stage would add utility (while the IEUBK model considers children only up to age 7, a PBPK model could be used to examine girls around 12 years of age). I do not know if the elevated BLLs reported in these studies were associated with exposure during the 0-7-year life stage, but modeling girls around the age of puberty to examine how their BLLs are affected by lead in drinking water (as well as other sources) may be informative. Exposure scenarios—drinking water only: Since the focus of this effort is to develop drinking water standards, I think presenting the results from a drinking water only scenario is helpful. Although this is likely not realistic (exposure will come from other sources and it is unlikely that the baseline BLL will be zero), this scenario would be useful in evaluating how incremental changes in lead water levels will affect the baseline BLL. This scenario would probably also be applicable to the 0-6-month life stage for formula-fed kids, where most exposure would come from tap water. All pathways: This is the most useful scenario as most children will likely have multiple exposure sources (and some will have greater exposure from soil or dust than water) and the contributions of each of these to the overall BLL should be evaluated. Maternal blood lead should be given more consideration as this will obviously affect the baseline BLL in the child. Target BLLs: The consideration of the two BLLs is reasonable; these are the current CDC criteria for elevated BLLs. As this effort is concerned with developing drinking water standards, it is important to understand how changes in water lead concentrations will affect these baselines BLLs. While the analysis of the probability of exceeding this level is useful (Approach 1), I think it is more useful to understand how water levels will incrementally increase the baseline BLL (Approach 2). Approach 1 is supposed to answer the question of what Pb water concentration will increase a child's probability of having an elevated BLL. Any increase in exposure above the baseline BLL will increase the probability of having an elevated BLL; it just seems more practical to evaluate the increase in BLL resulting from various water concentrations of lead. Another approach that may add utility is to run the models using "feasible" or "target" water lead concentrations to examine how these affect the BLLs (as well as varying the

[1] N Engl J Med. 2003 Apr 17;348(16):1527-36. **Blood lead concentration and delayed puberty in girls.** Selevan SG[1], Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J.

Environ Health Perspect. 2010 Dec;118(12):a542. doi: 10.1289/ehp.118-a542b. **Do metals meddle with puberty in girls? Lead, cadmium, and altered hormone levels.** Betts KS.

Environ Health Perspect. 2003 May;111(5):737-41. **Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994.** Wu T[1], Buck GM, Mendola P.

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	baseline contributions to overall lead exposure). Also, it would be helpful to run these models with a specified population (i.e., one that has higher exposure from water—for example, homes that have lead-based paint are also likely to have higher lead levels in soil/dust and drinking water) so examining the model outputs for these special populations might be useful. When more data become available for homes/schools with lead service lines (and also on how seasonal variability in lead concentrations affect the home/school concentrations and thus exposures), these data should be incorporated in order to understand how this will affect the child's BLL. A "worst-case" scenario should also be evaluated (i.e., highest soil/dust/food concentrations along with high water concentrations) in order to understand the risk that this could pose to a highly exposed child. As lead concentrations in water are transient, an additional approach that might be useful is to model varying periods of time (24 hrs, 1-2 months, and 6 months to a year) and then compare the results and how the changes in lead concentration over time affect the BLL.
Nascarella	The *age* range is generally appropriate (infants to 7-year-old children). Formula-fed infants are the most susceptible population, and this life stage is sufficiently captured using the presented approaches. The document should describe, in a quantitative manner consistent with the currently presented analyses, why pregnant women and fetal exposure (from maternal lead) is not otherwise considered. At relatively low levels of maternal exposure, lead is associated with hypertension, premature delivery, and spontaneous abortion. While the IEUBK model is limited in the ability to model this scenario, this should not preclude its consideration. It did not preclude the use of the Adult Lead Model. It may be useful to develop specific guidance for exceedances at schools (i.e., consider children > 5 years old). In this specific guidance, considerations should be given to the fact that total water consumed at schools is roughly 50% of that of residential use. The analyses should be conducted in a manner to consider elevations of water lead levels at specific taps. For example, an approach that describes how a fraction of the total daily consumption of water (~0.15L), might compare to an estimate derived from consuming all water (~ 0.600L) from one source might be useful. The approach to use *target* BLLs in the manner described is confusing. As presented, this outcome is neither "health-based" nor a true benchmark. Biomonitoring of lead in blood are measures of *exposure*, not measures of *health effects*. Additionally, the term benchmark has been widely adopted as a term that refers to a dose-response modeling approach to estimate a point of departure, upon which to base a health-based criterion. To use the term *benchmark* here implies that 3.5 µg/dL or 5 µg/dL is a *benchmark response* that corresponds to a *benchmark concentration* of lead in water. This adds confusion to an already exceedingly difficult conversation about lead in drinking water, and will serve to distract from the goals of this endeavor (an analysis to inform public

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	education requirements, and risk mitigation actions at the household or school level). Further discussion on this point follows in more general comments. As blood lead levels are not measures of "effect", the upper tail(s) of the distribution of NHANES data describing blood lead levels should not be interpreted as a health-based criterion or "targets". These are exposure measurements and not health-based thresholds of effect. As the EPA modeled approach is focused on shifting a "baseline probability distribution of blood lead for an individual", the sensitivity of selecting the tails of this distribution (3.5 and 5.0 g/L) and not a central tendency estimate should be explored.
Ryan	EPA has spent a good deal of time evaluating life stages for exposure over the last decade or more. The Agency developed a much more nuanced approach with many more categories than the three given here. However, for the purposes of this work, it would seem that the lifestages here are reasonable. The authors must make a strong argument for choosing these collapsed life stages over those proposed by the Agency in the past. Nevertheless, there will be argument from other parts of the Agency suggesting alternatives to the selected life stages. These arguments are likely mitigated, however, by the selection of exposure factors that vary only weakly with age. See discussion below. <u>0-6 Months Life Stage</u> In this age category, scenarios are evaluated based on use of infant formula, formulated using tap water, as supplementation during breast-feeding, or in exclusive use. Exposures within this age group are dominated by this formula/tap water intake. Children at this age are less mobile than at later stages and are unlikely to experience significant non-tap water exposures. One may argue that breastmilk exposures may be substantial as well. Some work carried out in the early 1990s (Hu, et al.) suggested that breast milk may also contribute to lead exposures as lead is mobilized from bone stores in pregnant and lactating women. However, presupposing breastmilk contributions with no higher concentrations than those found in drinking water would mitigate any exposures to being comparable; intake of breastmilk with lead levels equivalent to tap water would be supplemented by tap water/formula at essentially the same level. If breastmilk levels were lower, then exposure overall would be decreased. <u>1-2 Years Life Stage</u> By age six month, infants are beginning to make the transition to exploring the world and by 1 year they are fully into this process. Through the age of 2 years, mouthing and other similar activities play an important role in the young child's exploration of her or his surroundings. Locomotion is often accomplished by crawling activities early in this life stage and by walking later. However, in both cases, the child is still close to ground levels and likely to experience more contact with house dust, primarily, and soil later, as outdoor exploration begins. Dust and soil intake becomes a contributor - at some points the major one - in this life stage. One may reasonably argue about the boundaries of this life stage. Should it be 9 months and 3 years, for example. Again, this is a choice

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	that needs to be made. There is support for the 1-2-year life stage that is justifiable. I do not believe that an alternative selection would be any more defensible - just different. I cannot argue persuasively for this particular parsing of life stage, nor can I argue persuasively for any other specific parsing. <u>0-7 Years Life Stage</u> I have the most difficulty with this "life stage" as it encompasses a very broad span in maturity. The authors already believe that 0-6 month differs from 1-2 years as evinced by the separation of those two time periods. Now we see an expansion throughout both these ranges and on through childhood. Exposures differ substantially over this life stage and the parameters needed to model this diverse-activity stage vary widely. For Approaches 1 and 2, a measure of central tendency is used, but exposures are likely diverse across the range. In fact, the authors show this and use a weighted average of age-specific values to develop a single parameter for this life stage. On the positive side, however, the point of this life stage is to evaluate cumulative exposure (in the dictionary sense, not the FQPA 1996 sense) experienced by the child that may influence long-term effects such as neurodevelopment, which extends over much of this range, social development, and psychological development, which includes this life stage range and far beyond. Exposures and effects are likely highly variable. Because of this, stochastic simulation approaches such as SHEDS may offer a better evaluation of the impact of exposures on this life stage versus the shorter-duration early life stages. <u>Other Life Stages</u> Once children enter school, social development comes into play to affect exposures. This continues onward to older ages, e.g., early and later adolescents and the reduction of soil and dust based exposure and perhaps the beginning of occupational exposure and long-term effects such as hypertension. Further, effects may be gender-specific as children age through early childhood to pre-pubescence and adolescence. There is little evidence for gender-specific lead-based exposure early on, but one may be inclined to examine this as well. ***After discussions with my colleagues at the meeting I am more concerned with the lifestages selection. I maintain my acceptance of the 0-6-month lifestages as being important, but also see the need for understanding more about <u>in utero</u> exposures. This is, of course, dependent on the mother's exposure, which I believe should be an important consideration in the modeling work. Models should be developed to relate the drinking water intake of the mother with fetal uptake. This may be most important in the first trimester and during other specific time periods during gestation when the neurological system is under development. The breastmilk/formula period is most important in this regard, and would be effectively covered by the 0-6-month scenario. However, the 6-18-month period is still one of rapid change in the neurological system, which is likely still quite affected by intake of lead and other lead-based exposures. EPA should evaluate alternative modeling strategies during these critical time periods.***

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	An additional discussion focused on the 0-7 lifestage. While many comments were similar to mine given above, there was additional discussion of the 4-5, or 4-6-year age group. My thoughts would be to split the 0-7 age group into 0-4, and 5-7 to account for expected differences in likely routes and pathways of exposure consistent with change in social and developmental stages. Scenarios Drinking-Water Only - Since the main focus of the modeling effort is the assessment of a new drinking water standard, is worth the effort to evaluate the incremental effect of drinking water above and beyond the effects of other exposures. Further, it is also important to see the overall effect of all aggregate exposure (now in the FQPA 1996 sense) to lead to determine the impact of drinking water on overall effect. For example, if drinking water totally dominates exposure, and thus effect, evaluation of other exposures is not warranted. If the converse is true, then the effect of modifying a drinking water standard would be negligible and would incur a cost not warranted by the benefit. Hence one most evaluate both of these scenarios. The two BLL scenarios are warranted. The current "level of concern" for BLL is 5 µg/dL, hence that is a good modeling baseline. The analysis of the probability of exceeding this standard given a specific value for the drinking water standard is an appropriate value. Further, if a new standard were adopted, say 3.5 µg/dL, it is important to understand water-concentration impact on that standard. Should a new standard be adopted by CDC for BLL, 3.5 µg/dL is as likely as any other, given that current thought is that effects are likely to be observed at levels down to zero. But 3.5 µg/dL is probably about what one can hope for as a reasonable standard. Given these observations, the modeling parameters seem appropriate. One may argue for other standards, e.g., say 2.5 µg/dL or even 1.0 µg/dL, but the feasibility of getting either of these values at the 5%, 2.5%, or 1% level is fraught with difficulty. From a public health perspective, I would like to see a 1.0 µg/dL at the 95% level implemented, but is this really feasible currently? Probably not. ***My thoughts were not substantially modified during our discussions. There was a good deal of discussion back and forth on the Drinking-Water Only Scenario. I believed prior to the meeting, and I was not dissuaded by the discussion, that this is useful for the development of the models for drinking-water standards. In my opinion, the utility of a modeling system that could explore the incremental effect brought on by drinking water alone is an important consideration and should be maintained.***
Vork	Comment: The work presented in materials provided to the panel members describes three valuable approaches for assessing the role of water concentrations of lead on blood lead levels of infants and young children. These approaches all have merit in screening for potential hazards and informing risk managers and the public. The following comments mainly seek clarity to this effort. To begin, some clarifying objectives for this

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	research goal would help focus comments on the merits of current work and/or how this work could be strengthened. For example, health implications such as decrements in IQ have been associated with increments in lead drinking water levels (OEHHA PHG 2009). For infants who are exclusively bottle fed with formula reconstituted with tap water, this is expected to be a major source of lead exposure. For this vulnerable population, here are some possible objectives: Develop approaches that can derive: 1) a level of lead in water used to reconstitute commercial formula that would raise a) the probability of infant blood lead levels changing by, for example, 1% over the first six months of life; b) an infant's blood lead level by, for example, 1 ug/dL over the first six months of life. 2) a change in the level of lead in water used to reconstitute commercial formula that would increase a) the probability of infants' predicted background blood lead levels by, for example, 1% over the first six months of life; b) an infant's predicted background blood lead level by, for example, 1 ug/dL over the first six months of life. Another vulnerable group is children in their second year of life (ages 1 to 2 years). These children have exposure to other sources of lead and may change the level and form of tap water intake (e.g. less intake from reconstituted calcium-rich formula to tap water with and between meals). These changes could raise their blood lead levels closer to levels of concern. Hence, elevated levels of lead in tap water may result in exceedances of blood lead level of concern (e.g. 3.5 or 5 ug/dL). For this vulnerable population, here are some possible objectives: Develop approaches that can derive: 1) a level of lead in tap water that would raise a) the probability blood lead levels changing by, for example, 1% over the second year of life; b) a child's blood lead level by, for example, 1 ug/dL over the second year of life 2) a change in the level of lead in tap water that would increase a) the probability of children's predicted background blood lead levels by, for example, 1% over the second year of life; b) a child's predicted background blood lead level by, for example, 1 ug/dL over the second year of life 3) a level of lead in tap water that would reduce to (e.g. 1-or 5%) the probability that blood lead levels in a similarly exposed population would exceed a level of concern over the second year of life A third group of vulnerable children are those who are still very young but are now spending more time outdoors and away from home (i.e. ages 2 to 7 years old). These children have exposure to other sources of lead and may change the level and form of water intake (e.g. less intake from household tap water with and between meals).

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	These changes could raise their blood lead levels closer to levels of concern and increase the day-to-day level of exposure. Hence, smaller increases of lead in household tap water may result in exceedances of the blood lead level of concern (e.g. 3.5 or 5 ug/dL). For this vulnerable population, here are some possible objectives: Develop approaches that can derive: 1) a level of lead in tap water that would raise a) the probability blood lead levels changing by, for example, 1% over ages 2 to 7 years; b) a child's blood lead level by, for example, 1 ug/dL over ages 2 to 7 years 2) a change in the level of lead in tap water that would increase a) the probability of children's predicted background blood lead levels by, for example, 1% over ages 2 to 7 years; b) a child's predicted background blood lead level by, for example, 1 ug/dL over ages 2 to 7 years 3) a level of lead in tap water that would reduce to (e.g. 1-or 5%) the probability that blood lead levels in a similarly exposed population would exceed a level of concern over ages 2 to 7 years Consider modeling the second 6 months of life for infants. For this age group, similar BLLs to those predicted for the 0 to 6-month age group were predicted by the IEUBK model using default parameter values and set to percent above 5 ug/dL. However, the 0 – 12-month exceedance were slightly less (% above 13.8, 13.4 and 11.2 for the 6 to 12, 0 to 6 and 0 to 12-month groups respectively). The IEUBK model allows for changes in GSD up to 1.8. However, the combined GSDs of 1.6 for biological and 1.6 for environment variability exceed 1.8 (Exp(sqrt(ln(1.6))^2 + (ln(1.6))^2) = 1.944. There are some sources of variability and uncertainty that may need to be addressed for each age group. For example, 1) Some factors that could influence blood lead predictions for 0 to 6-month infants might be level of "hardness" in the water, calcium in formula and lead in maternal blood. 2) Some additional factors that could influence blood lead predictions for the 1 to 2-year age group might be the history of blood lead in infancy and uptake of lead from food and residential soil and dust. 3) Some additional factors that could influence blood lead predictions for the age 2 to 7-year age group might be the history of blood lead in earlier childhood and uptake of lead from food and nonresidential soil and dust.

1.2 MODEL INPUTS

Please comment on the strengths and weaknesses, including suggestions for improving the input parameters (i.e., point estimates and distributions) for the IEUBK and SHEDS-IEUBK modeling approaches. Please identify any data gaps or additional data related to the various input parameters that could improve the exposure and BLL estimates. Please

comment on the appropriateness of the water consumption rate based on NHANES data for this modeling effort, and on soil/dust ingestion rate and other key factors.

Reviewer	Comments
Georgopoulos	Though model inputs are generally reasonable, what matters is the context in which they are used and the interpretation of the outputs they produce. As was mentioned in the response to Question 1, applying IEUBK with input values that represent measures of central tendency (such as the geometric mean) for various exposure-related variables/parameters of the model, does not necessarily produce corresponding outputs that also represent measures of central tendencies of distributions of these outputs; this is important when trying to interpret the outcomes from Approaches 1 and 2. However, even in the distributional/probabilistic application employed in Approach 3, it is not clear how all the, potentially significant, correlations between exposure-relevant input parameters are taken into account. These correlations are expected to be especially significant for the most highly exposed individuals within the population simulated, and therefore to affect the upper tail percentiles (95% and 97.5%) that are derived in Approach 3. SHEDS can employ a "bottom up" approach that assembles individual information from databases to build empirical distributions of exposure factors that could capture correlations if appropriate sampling rules are used. However, the descriptions of "Inputs for IEUBK-SHEDS Coupled Analysis," in Exhibits 13-20 (pages 33-40 of the document under review) refer to the empirical distributions summarized in Exhibits 4-10 (pages 21-30 of the document), generally without providing information on how correlations are treated. There are certain statements, such as "in SHEDS the input for time spent outdoors also impacts the soil and dust ingestion rate, as well as soil and dust exposure," on p. 22 of the document, but it is not clear how this impact - especially on the rate, rather than on the cumulative intake - is quantified in the calculations. On the other hand, on p. 27 of the document, explicit information on correlations used in modeling inputs is provided: "In conducting the SHEDS-IEUBK approach 3 analysis for soil lead concentration, an empirical distribution was fit to data provided by HUD from AHHS (HUD, 2011). The data were stratified and weighted by house age pre- and post-1950, and a correlation coefficient of 0.48 between dust and soil lead concentrations was assigned in SHEDS. A correlation coefficient of 0.2 was also applied to the water and dust concentration distributions, based on EPA's NHEXAS study Clayton, Pellizzari, Whitmore, Perritt, and Quackenboss (1999)." Given the importance of correlations on results corresponding to the extremes/tails of the output distributions, it is recommended that all correlation rules used in the SHEDS-IEUBK simulations are explicitly listed and summarized in a table. However, there is still a variety of other issues with data limitations. One example is that contributions to lead levels in water from distribution system service lines versus premise plumbing are not separated. Another example involves the use of dust lead concentration inputs from AHHS mentioned in the previous paragraph of the present response, in relation to dust/soil lead correlations; specifically, on p. 26 of the document it is stated that: "[o]f the 5,612 floor dust wipe samples taken during the survey, only 404 were above the detection limit of 5 μg/ft^2. However, raw analytical data files were obtained by HUD from the laboratory processing the floor wipes, which included some of the samples below the level of detection, resulting in 1,131 dust wipe samples with

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	data available to calculate dust lead levels. These additional data points were used by HUD in the calculation of the mean values for dust lead from floor wipes. According to HUD, "this procedure provides unbiased estimates of means, provided that measurements below the detection limit are normally distributed about the true value of the analyte, as is generally assumed in discussions of the detection limit" (HUD, 2011, p. 43)." The statement from the AHHS report (HUD, 2011, p.43) that is provided in quotes in the document under review, is actually attributed to the first edition of the textbook by Helsel (2005); however, this assumption of normality is not necessarily used in the treatment of non-detects in other modeling inputs in the present effort currently under review (and is a potentially important issue, as the actual percentage of samples above detection limit is only around 7%). Furthermore, the fact, quoted on p. 27 of the document under review, that "dust lead concentration is assumed to be correlated with soil lead concentration and that both tend to be highly variable in different areas of the United States" points (as mentioned in the response to Question 1) to the potential usefulness of performing and comparing simulations for specific physiographic etc. regions of the US. Finally, another example of problematic inputs (or data gaps that can affect outcomes) can be found on p. 28: "Zero- to 6-month-olds and 0- to 1-year-olds were assumed to have the same soil and dust ingestion rate as 1-year-olds due to lack of data." It should be mentioned that various input data limitations are indeed explicitly recognized and discussed in the document under review. For example, on page 50 it is stated that "there are limitations and uncertainties with some of the inputs associated with both the IEUBK and SHEDS model" and that specifically "there is a limitation in using point estimates for the absorption fraction of lead from the different environmental media." However, the values used are consistent with what is currently used in the IEUBK model. Further, there is no drinking water intake value specific to formula-fed infants in the NHANES data that are used in SHEDS, and therefore the population that the NDWAC suggested considering is not explicitly considered in this approach. It is also unclear the extent to which the underlying distributions in the SHEDS model, as well as the NHEXAS-derived correlations between distributions in the SHEDS model, are accurate representations of those found in the U.S. population." Such discussions within the document under review are indeed useful; the USEPA should consider summarizing/ organizing such points (involving data limitations and gaps) either in stand-alone tables or in additional columns of the tables ("Exhibits") describing the modeling inputs. It appears the NHANES water consumption data have been used for the input distribution of water consumption rates, instead of the (substantially different) distributions provided in USEPA's Exposure Factors Handbook, in order to allow comparisons of SHEDS-IEUBK BLL outcomes with NHANES BLL levels. As recommended earlier, in the response to Question 1, it would be very useful to perform SHEDS-IEUBK simulations and compare calculated BLL outcomes using EFH water consumption rates to those calculated using NHANES water consumption rates.
Goodrum	Each of the three modeling approaches uses a set of inputs to generate BLLs that reflect multi-media exposures. In the case of Approaches 1 and 2, only point estimates are used, and in Approach 3, a combination of point estimates and probability distributions

Reviewer	Comments
	are used. Importantly, the results are "ground-truthed" by comparing the predicted BLL distributions to BLL distributions reported from NHANES (e.g., Report p. 19). As explained in greater detail below (comments on Charge Question 3), an alternate approach that uses distributions from NHANES more directly in the modeling may be preferred. This can greatly simplify the analysis while remaining grounded in data-driven evaluation of the key questions regarding the drinking water exposure scenario. If my recommendations are accepted, then most of the input variables are no longer needed, and one can focus specifically on the drinking water exposure variables. So my comments focus on these variables, but I also add thoughts on the maternal BLL and GSD (which would both still be needed), and the soil and dust ingestion rate, one of the more influential variables in the three approaches described in the report. **Drinking Water – Water Consumption Rate (L/day)** Exhibit 6 of the Report summarizes the age-group-specific input values used for average daily water consumption rate. I have the following comments: • GSD calculation – all the values shown in Exhibit 6 need to be recalculated. As reported, they range from 0.0025 to 0.0035, which is not possible. Please double check your equations. Based on the other summary statistics that are reported, GSD likely ranges between 1.5 to 2.4 across age groups. Refer to Zartarian et al. (2017, Table S3) for GSD values that range from 2.5 to 3.5 – these seem high if in fact the other summary statistics in the table are correct and the distribution is approximately lognormal. • The GM values (bolded in Exhibit 6) are used/proposed mainly to conform with the SHEDS model inputs, but EPA expects that central tendency inputs to the IEUBK reflect the arithmetic mean (AM) (USPEA 1994a). While I agree that updating the standard default values in IEUBK makes sense because the current defaults are based on much older survey data, the difference between the AM and GM is considerable and should, at a minimum, be highlighted in a sensitivity analysis. See Table 2 below for side-by-side statistics including the current standard defaults in IEUBK (which rely on analyses performed on survey data from the late 1970s), the Report Exhibit 6 (based on NHANES 2005-2011), and EPA's 2011 Exposure Factors Handbook (EFH) recommendations (based on both USDA's dataset from 1994-96 and 1998, and NHANES 2003-2006). Table 2. Summary statistics for consumption rates (L/day) of tap water (all uses). IEUBK Defaults[a] / Exhibit 6[b] / Exhibit 6 / EPA 2011[c] Age Group / Mean / Mean / GM / Mean 0 to < 6 months / 0.20 / 0.662 / 0.526 / 0.287[d] 0 to < 1 years / 0.20 / 0.581 / 0.410 / 0.324[d] 1 to < 2 years / 0.50 / 0.247 / 0.151 / 0.271

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2 to < 3 years	0.52	0.300	0.176	0.317
3 to < 4 years	0.53	0.316	0.193	0.327[e]
4 to < 5 years	0.55	0.320	0.197	
5 to < 6 years	0.58	0.364	0.213	
6 to < 7 years	0.59	0.377	0.228	---

[a] IEUBK defaults are based on USEPA EFH as of 1994, which largely relies on national survey data collected by USDA from the U.S. population in the late 1970's, as summarized by the EPA 1989 EFH.

[b] Exhibit 6 relies on NHANES 2005-2011 for all age groups.

[c] EPA's 2011 EFH relies on USDA's Continuing Survey of Food Intake of Individuals (CSFII) survey (1994-96 and 1998) for age groups < 3 years, and NHANES 2003-2006 for older age groups.

[d] EPA's 2011 EFH (Table 3-1) provides per capita means for ages 0 to < 1 month (0.184 L/day), 1 to < 3 months (0.227 L/day), 3 to < 6 months (0.362 L/day), and 6 to < 12 months (0.360 L/day). Values shown here are simple arithmetic means of 6-month and 12-month periods, after distributing monthly data based on the means reported.

[e] EPA's 2011 EFH (Table 3-1) provides per capita mean for 3 to < 6 years.

The following observations are clear from the side-by-side summary statistics:

- Given that each of the reported distributions of water consumption rates is positively skewed, the GM is a lower metric of central tendency than the AM. Therefore, the decision to rely on the GM instead of the AM as an input in IEUBK model runs will yield lower estimates of exposure from the drinking water pathway. Based on Exhibit 6, the GM would be expected to yield between 20% to 40% lower exposures.

- The Report (p. 24, footnote 9) explains that the inputs selected for this analysis are different from EPA EFH recommendations – higher for children younger than 1, and lower for children age 1 and older. This is only partially true. It would be helpful to add the percent difference in this explanation. For the children younger than 1, use of the more recent NHANES results supports estimates that approximately 57% higher for 0 to less than 6 months, and 44% higher for 0 to less than 1 year. For ages older than 1 to less than 5 years, the more recent NHANES results are lower than EFH by 2% to 10%. For ages 5 to 7 years, the more recent NHANES results are higher than EFH by approximately 10%. Therefore, for the 0-7 year age group, the more recent NHANES results are approximately the same (within 10%) of the inputs recommended in EFH.

I support the use of the more recent NHANES results as reported in Exhibit 6, however, the AM rather than GM values would be more appropriate for the scenarios used in the final derivation of a health-based benchmark.

Maternal BLL (µg/dL)

The Report (Section 5.10) provides a good justification for using a maternal BLL of 0.61 µg/dL in lieu of the current IEUBK default of 1.0 µg/dL.

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	GSD (unitless) A default GSD of 1.6 is typically used (and recommended by EPA) when applying the IEUBK model (USEPA 1994a,b). The value was derived from several epidemiological studies and further tested by Hogen et al. (1998), who determined that observed and predicted probabilities of EBLL (defined at the time as > 10 µg/dL) matched to within 4%. In these applications, it is important to recall that the GSD is the amount of variability in BLLs among children exposed to similar concentrations of environmental lead (USEPA 1994a; White et al. 1998). This is actually noted in the Report on page 14. For this reason, it is sometimes referred to as the "individual level GSD". It is a lumping term intended to account for exposure variability (except for the concentration term), biological variability, and measurement error. Note that Zartarian et al. (2017, p. 10) state that the GSD of 1.6 does not account for exposure variability, which is not true – as stated above, it accounts for essentially all of the exposure variability (e.g., activity patterns, hand-to-mouth behavior, media ingestion rates, etc.) except for the variability in concentrations across different households. In the Report (Section 5.11), the GSD of 1.6 is used for Approaches 1 and 2 for all age groups except infants. The analysis presented to support a lower GSD of 1.45 for infants 0 to 6 months is good and makes sense. Approach 3 does not explicitly use a GSD, but rather relies on Monte Carlo simulation to propagate variability from multiple sources of exposure. There are several challenges for the different method used in Approach 3: 1. Variability in environmental concentrations is explicitly used, in contrast to the typical applications of IEUBK for which the goal is to represent variability in BLLs among children exposed to similar concentrations. This is done with the intent of representing variability in BLL on more of a national scale. 2. A child's exposure is simulated over time, using a series of short model time steps. With each time step, a new random value is selected from a set of probability distributions. If no correlation structure is applied to address intra-individual variability, then the shorter the time step, the greater the number of random values needed over a fixed exposure period (see comments on Charge Question 5 for more discussion). This has the effect of making each simulated child look more like the average child. Zartarian et al. (2017) settled on a 30-day averaging time. EPA explained that this means that results over a 30-day period are used to represent each of the age groups – so it is a decision about how to package the output (i.e., predicted blood lead distribution). EPA further explained that the time series is given by the diary information input to SHEDs, and that for each simulated child, approximately 4 to 5 random values are selected for each variable that is represented by a probability distribution. The process for implementing this micro-exposure event simulation in the Monte Carlo Analysis requires further explanation in the report because this was not at all clear to me prior to the public meetings.

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	In the report, the implications of the time step needs to be explained in terms of the real effect that this has on the variance of the distribution. For example, if soil and dust ingestion rate is represented by a lognormal distribution with a specified arithmetic mean and standard deviation, then the process of selecting 4 or 5 random values (for each hypothetical child) has the effect of reducing the arithmetic standard deviation by the square root of n, or approximately a factor of 2 (i.e., sqrt(4) = 2; sqrt(5) = 2.2). This should be shown both graphically and in a summary table whereby the parameters of the "initial distribution" are given, and the parameters of the "effective distribution after random sampling" are also provided, assuming 4 to 5 random values are drawn. For example, consider the soil and dust ingestion rate for the 1-year old, which Zartarian et al. (2017, Table S3) indicates is represented in the Monte Carlo simulation using an empirical distribution with the following parameters: • Arithmetic mean = 43.9 mg/day • Arithmetic standard deviation (SD) = 54.8 mg/day • GSD = 2.8 (empirical PDF), or 2.6 if fit to a 2-parameter lognormal (mean, SD) Assuming this distribution is sampled at random 4 times, the resulting distribution will have the following parameters (on average): • Arithmetic mean = 43.9 mg/day • SD = 27.4 mg/day • GSD = 1.8 if fit to a 2-parameter lognormal (mean, SD) That is, the effect of averaging the 4 or 5 random values is equivalent to sampling once from the distribution with the smaller SD. Given that the sensitivity analysis confirmed that the soil and dust ingestion rate parameter is one of the more influential variables on the predicted blood lead distribution, this reduction in variance that is attributable to the resampling will likewise have an effect on the GSD of the blood lead distribution generated by the Monte Carlo simulation. Below is an example graphic that shows the original distribution (in blue) fit to a lognormal PDF and the distribution after resampling with n=4 random samples (in pink). The top graphic is the PDF view and the bottom graphic is the equivalent CDF view.

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	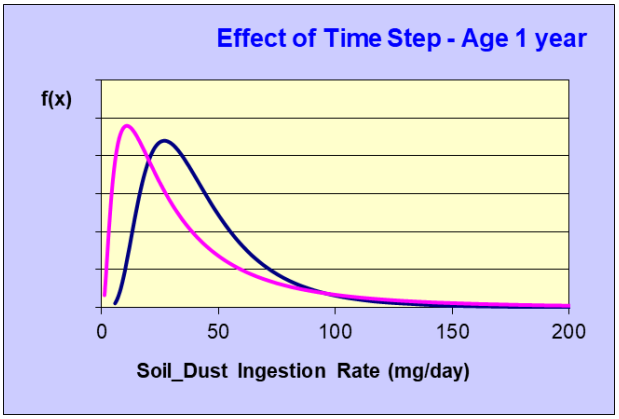 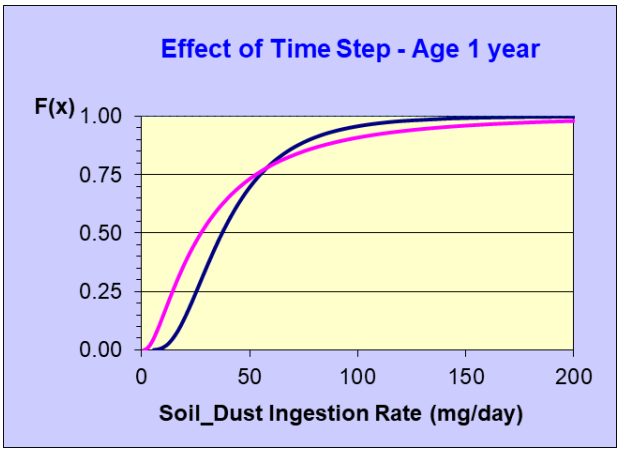 EPA also indicated truncation limits were imposed on the empirical distributions based on the survey results as entered into SHEDs. These truncation limits should be noted in a summary table in the report, along with the other summary statistics. The main point is that different time steps (or numbers of random draws from the distribution) will yield different results, and serial (repeat) measurements of the same study population are typically not available to resolve this source of uncertainty. So the choice of time step, although derived from diary information, is still an extrapolation uncertainty because we are using short term survey data to represent long-term average behavior. This uncertainty has a direct effect on the uncertainty in the GSD of the simulated blood lead distribution. The effect of resampling should be conveyed for all of the variables that are represented by PDFs in the Monte Carlo simulations. 3. Approach 3 does not capture biological variability, so an adjustment procedure is applied, guided by a comparison to the GSD from NHANES BLLs. Clearly Approach 3 is more complicated than approaches that rely on a user-defined GSD, requiring many decisions as far as distributions specified for input variables, model correlation structure and time steps, and adjustment factors to specify variance in BLLs.

Reviewer	Comments
	At the end of the day, given the specific charge question (developing a health-based benchmark for lead in water), the GSD of 1.6 seems to be better positioned to represent the aggregate sources of variability. Uncertainty can be represented by showing results for a range of GSD's that bracket 1.6 and perhaps low and high ends based on EPA's experience in lead risk assessments at specific communities. See comments on Charge Question 3 for additional discussion on the strengths and limitations of the proposed approaches. **Soil and Dust Ingestion Rate (mg/day)** The contribution to BLL from non-drinking pathways need not be explicitly modeled, as discussed in my comments to Charge Question 3 below. However, if these pathways are modeled, the following feedback is provided on the inputs that are proposed (Report Section 5.8). Similar to the water consumption rate variable, the input values for soil and dust ingestion rate are guided by the values used in SHEDS (in order for Approaches 1, 2, and 3 to be comparable), rather than by a true recommended set of age-specific inputs. In addition, similar to the water consumption rate variable, the GM soil and dust ingestion rate is used in favor of the AM – EPA indicates in the Report (p. 28) that this is justified because use of the AM yields a predicted BLL that is much higher than national averages. So again, NHANES data are used to evaluate the plausibility of the model BLL predictions and thereby ground-truth the choices for inputs. It is unclear why/how a difference between NHANEs and BLLs can be attributed to a single exposure variable. The Report includes references to Özkaynak et al. (2011) and von Lindern et al. (2016) and indicates that the different methods used by the separate investigation teams support similar values for older ages. Furthermore, the Report states that Özkaynak et al. is preferred because it provides a distribution, as opposed to a point estimate, for each age group considered. I question this logic since von Lindern et al. certainly supports probability distributions for each of the age groups as well (see von Lindern et al. 2016, Supplement Table S-1). Özkaynak et al. (2011) uses an activity pattern modeling methodology to estimate soil and dust ingestion rates. EPA reviewed this study in the 2011 EFH (Section 5.3.3.5) and identified a primary limitation as lack of data to support inputs for some of the variables used in the estimation including: • activity patterns of children in younger age groups, including children with high hand-to-mouth, object-to-mouth, and pica behaviors; • information on skin adherence; and • information on dust loadings on indoor objects and floors. In addition, EPA 2001 EFH (p. 5-16) cites Özkaynak et al. (2011) results for ages 3 to < 6 years, but not other age groups of interest due to lack of data.

Reviewer	Comments
	von Lindern et al. (2016) used a comparison of community-specific measured BLLs to predicted BLLs based on IEUBK model runs with site-specific exposure factors. More than 3,000 children participated in the study. A major benefit of this approach is that it relies on BLL, which is a time-integrated exposure metric, so there is no uncertainty associated with extrapolating from short-term survey results to long-term average behaviors. The main limitation of the analysis of the Bunker Hill community data by von Lindern et al. (2016) is the potential low bias introduced due to public awareness and community interventions to reduce exposure to lead. It is acknowledged that the awareness of lead exposure may have changed parental supervision of children, thereby reducing soil and dust ingestion. I suspect that the normal hand-to-mouth behavior of young children would not have been altered, but perhaps the parental influence on outdoor play areas and housekeeping to reduce indoor dust exposure could have introduced a low bias for some period of time. Given that a site-specific estimate of bioavailability was accounted for, the uncertainties associated with specification of other exposure factors in the model are minor in my opinion. The bottom line is that, between these two studies, I believe the von Lindern et al. (2016) estimates of childhood soil and dust ingestion rate would serve as a more supportable source. Their use of the IEUBK model to adjust soil and dust ingestion rate in order to optimize the fit to the measured BLLs is scientifically sound, reproducible, and builds from a methodology that has a long track record of use in human health risk assessment. Note that since the public meeting, another relevant article has been published, which uses the best tracer methodology (fecal tracer study) to estimate soil and dust ingestion rates for 177 children ages 2.5 to 12 years old living in three provinces in China (Lin et al., 2017). EPA may wish to consider this study as well in its analysis of the available literature.
von Lindern	As noted above, it is also difficult to provide meaningful comment on the appropriateness of the input variables without knowing the purpose of the model or how it will be used. The report notes that: "Due to the national scope of this exploratory lead modeling effort, and given the additional exposure modeling possibilities made available with the SHEDS tool, EPA modified several of the default inputs to the IEUBK model. The modified input values were developed from a number of national-scale data sources that were available to the Agency at the time this set of potential modeling methods were being developed. The selection and use of these input values are for illustrative purposes to allow for ease of comparison across model approaches. The purpose of this report is to obtain feedback on various lead modeling methods that can be used to characterize the relationship between lead in drinking water and children's BLLs. The input parameters used in this analysis do not represent high-end exposures." With regard to the short-term purpose of successfully emulating the NHANES blood distribution by modifying the IEUBK input variable values, and using these same inputs

Reviewer	Comments
	in individual IEUBK Approaches 1 and 2, the analyses show consistency in results. It would be surprising if this were not the case, as decreasing the intakes will reduce the blood lead estimates. Interpretation of the data also shows that modeled impacts of drinking water lead varies according to whether water lead, or other sources, is first input to the model. This result is also not unexpected. This is likely indicative of competent model structure and development. Nevertheless, the modifications to the IEUBK input parameters substantially change the outcome predictions in comparison to recommended EPA default scenarios; and have marked effect on any health-based benchmark that might be derived from the results. A simple comparison of the percent changes in key input values in contrast to the IEUBK default parameters shows the results are clearly biased toward effecting maximum water lead benchmark concentrations. The following Table from Exhibit 17 shows that the modifications to IEUBK inputs reduce the default soil and dust lead intake by 93%, diet by 88% and air lead by >90% allowing the water source to accommodate substantially more lead, and markedly increasing the "health benchmark level". **From Exhibit 17.** Variable / Input / IEUBK Default / Percent Reduction Inhalation: 3.82 / 5 / 24% Soil/dust Ingestion: 0.029 / 0.135 / 79% Water Intake: 0.193 / 0.53 / 64% Air Pb: 0.01 / 0.1 / 90% Soil Pb: 37 / 200 / 82% Dust Pb: 72 / 150 / 52% Diet Pb: 0.27 / 2.26 / 88% Maternal Pb: 0.61 / 1 / 39% Soil/Dust Pb Intake: 1.6 / 23.3 / 93% EPA justifies these substantial modifications by noting that i) application of the default input variables predicts mean blood lead levels substantially greater than those observed in the NHANES surveys; ii) the default values are out of date, iii) the intent is to rely on national databases previously used in the SHEDs analyses, and iv) the use of geometric means to characterize typical exposures, also consistent with SHEDs. *Over-prediction by Default Values:* It is not unusual for the EPA recommended default parameters to overestimate typical blood lead levels in numerous settings. EPA notes that most of the IEUBK default values were determined during the "Superfund Era"

Reviewer	Comments
	when blood lead levels were higher. In addition, several of the input default recommendations were conservative and were applied in the absence of site-specific data, such as soil and dust concentrations, which EPA encouraged be obtained. EPA has also developed the Exposure Factors Handbook to provide typical values for exposure co-factors to be used in risk assessment and mitigation, also in the absence of credible site-specific data. *Out of Date Values:* It is common, in fact encouraged, in IEUBK analyses to substitute credible site-specific data for the default values. This is particularly the case for media concentration and absorption variables that usually vary by site and can be directly measured. It's less common to modify the consumption variables as this implies that the population's habits and practices are site specific. Although the default media concentration values may need updating to reflect current exposures, it is less likely that children's incidental ingestion and water consumption habits have changed. In this report, EPA has elected to substantially modify these consumption, or exposure rate variable values, based on a desire to remain consistent with the national databases used to derive probabilistic variables for the SHEDS analyses. These databases have been noted to provide estimates lower than those relied on in the Exposure Factors Handbook and IEUBK model guidance and EPA has cautioned against using these sources in the past. Other EPA work groups are currently engaged in scientific reviews to update both the IEUBK and Exposure Factors Handbook recommendations. EPA should endeavor to see that those efforts and the development of the SHEDS model ingestion and water consumption estimates be consistent with each other and the recommendations of those advisory board findings. *National Data Bases and Geometric Means:* There are two main discrepancies among inputs in these analyses and typical IEUBK model applications: (i) the use of national databases that tend to underestimate exposure factors and exhibit large variances, and (ii) the use of geometric versus arithmetic means. Both are contrary to the development and evolution of the model and the published guidance. Simply substituting geometric means in the IEUBK inputs for these three key variables will inevitably reduce each source's contribution to the calculated mean blood lead estimate. In addition, the application of the 1.6 gsd in the model to derive exceedance estimates is an empirical compromise based on practice and observations spanning years of applications. This calculation of percent to exceed threshold values anticipates neither the lower central tendency estimates calculated from the geometric mean inputs, or the huge variances inherent in the national databases. Simple substitution of these values into the IEUBK, as accomplished in Approaches 1 and 2 may facilitate comparison to the SHEDs output, but nevertheless will produce spurious results. EPA notes in the report: "The selection of the geometric means for use in the two IEUBK-based modeling approaches is due to the lognormal distributions of the input data. Utilizing geometric mean input values differs from the use of arithmetic mean input values which were used in the evaluation of the IEUBK model. The IEUBK model results using geometric mean inputs are specifically intended for the purpose of comparing the utility of the three modeling approaches presented in this report and may not be generally applicable to other analyses. The selection of the

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	geometric mean for exposure rate inputs (water ingestion, soil and dust ingestion, and dietary intake) in this draft report should not be construed as a recommendation for their usage as an input parameter in the IEUBK model." This explanation is somewhat confusing, as the remainder of the report is an exercise in fitting the IEUBK to national blood lead distributions by substantially modifying the input parameters. EPA attempts to justify these modifications by comparing the variable distributions to national databases. However, in past efforts other EPA entities have cautioned against relying on these databases in developing both the Exposure Factors Handbook and recommended IEUBK input values. The IEUBK model has been developed to accommodate average exposures. Substantially modifying the intake rate inputs implies that the population (in this case the NHANES database) practices substantially different consumption habits than the populations anticipated in the IEUBK guidance. EPA identifies above the most troublesome rate inputs in the above quotation (water ingestion, soil and dust ingestion, and dietary intake). The water intake values used for older children is about 1/3rd of the IEUBK default recommendation. The large reduction seems to be related both to differences in consumption rates between the databases relied on, and on the use of the geometric rather than the arithmetic mean. EPA should discuss this selection in the context of the findings of Agency work groups and advisory committees currently engaged in scientific reviews to update both the IEUBK and Exposure Factors Handbook recommendations. EPA should endeavor to see that the Agency's characterization of the US population is consistent across programs, analyses, and development of health-protective measures, particularly as this is related to the drinking water standard. It seems EPA should be consistent across the Agency in its understanding of how much water US children consume. As EPA indicated, it is important to note that the selection of input values for soil and dust ingestion rate can have a significant impact on IEUBK model results, and the nearly 80% reduction in the soil ingestion rate is probably the most significant modification. EPA elected to estimate the soil and dust ingestion rate distributions by age based on models by Ozkaynak et al. (2011). This study predicted mean and 95th percentile total ingestion of soil and dust values of 68 and 224 mg/day, respectively; and indicated a total soil and dust ingestion lognormal distribution with geometric mean of 35.7mg/day and gsd of 3.3. Although it is unclear how the value was derived, EPA used a geometric mean of 26.6 mg/day in Approaches 1 and 2, stating: The geometric mean of 26.6 mg/day used in approaches 1 and 2 is less than the recommended EPA *Exposure Factors Handbook* (2011) "central tendency" values of 60 mg/day for individuals <1-year old and 100 mg/day for individuals between 1 and 21 years of age. A sensitivity analysis was conducted using the EFH central tendency value of 100 mg/day (by scaling the Ozkaynak et al. (2011) modeled distribution for the baseline runs). It was found in doing this that estimated BLLs were much higher than national averages, and therefore the input value of 100 mg/day was assumed to be too high for this analysis. The latter assumption is particularly troublesome, and it is questionable as to whether this justifies applying input values resulting in 93% reduction in lead intake. It is also

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	important to note that in SHEDS the much lower time outdoors value and the empirical relationship used to convert dust loading to dust concentration both further reduce the soil/dust intake rate. As noted above, the IEUBK default values often tend to overestimate observed blood lead levels. Both the Exposure Factors Handbook and IEUBK default values are consistently around the 100 mg/day for older children. More recent studies indicate typical ingestion rates may be closer to 60 mg/day. Both Ozkaynak et al. (2011) and this reviewer (von Lindern et al. (2016)), are cited in support of a 60-70 mg/day value. It is unclear how "scaling up" the modeled distribution was accomplished, but simply substituting 100 mg/day for the central tendency and employing the same gsd seems questionable. More important, however, is to remember that the lead uptake component in the IEUBK is the product of ingestion rate, soil and dust lead concentration, and bioavailability. It is also possible that the overestimation noted in the scale up analysis is due to the soil/dust lead concentrations or bioavailability used in the analyses. Both were input as point values, and much of the variation inherent in these variables may be subsumed in the large variation attributed to the ingestion rate. The relatively flat ingestion rate employed across all age groups is also troublesome. The use of the 1-year old rate for infants 0-6 months is likely inappropriate, especially considering that there is little difference among the ingestion rates used for all aged children, implying that formula-fed infants ingest as much soil and dust as 4-year-old children (Exhibit 9). Effective IEUBK analyses require careful specification of the soil/dust input variable. Children are exposed to various sources in their daily activities. Recent studies show that soil/dust exposure comes from within the home, home yard, play areas, neighborhoods and across communities. Each of these sources can have unique concentrations and bioavailability, and can vary independently. Relative contributions of these sources must be partitioned and proportional concentrations and bioavailability developed for the single individual inputs provided to the IEUBK. The variation should be captured by providing unique estimates for each individual input in batch mode. It is not uncommon that substantial contributions come from beyond the home, and are characteristic of the neighborhood and community. Older, less affluent, or industrial communities may present higher neighborhood and community soil/dust exposures for these children. The values are derived from the healthy homes surveys in this report, are limited in scope, and represent a broad spectrum of housing types and communities across the country with only two-point values. More effort should be applied in sensitivity analyses utilizing other ingestion rate inputs; e.g., von Lindern et al. (2016) has age-specific arithmetic means similar to Ozkaynak et al. (2011), but with larger geometric mean and much lower gsds. EPA did use the von Lindern et al. (2016) distribution for 2-year children in additional sensitivity analyses in the Supplemental Materials addendum to the recent EHP publication provided during the review period (EHP1605R2). These analyses could be enhanced by applying the technique to other age groups, as the 2-year old ingestion estimates in von Lindern et al. (2016) are the most uncertain and likely to over-predict blood lead levels. More sophisticated construction of the soil/dust exposure inputs should be developed, including consideration of community soils, and alternate dust lead concentration estimation. It is advisable to avoid drawing conclusions regarding the source of overestimation of observed blood lead levels in non-linear multiplicative models based

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	on manipulating a single variable. A more appropriate sensitivity analyses would to be use Exhibit 9 from the report for von Lindern et al. (2016) and apply it with a more sophisticated soil/dust lead concentration distribution.
Loccisano	Model inputs appear to be reasonable as they are based on data (and IEUBK model parameters are not simply fitted to data). However, correlation between input parameters (both the pharmacokinetic parameters in the IEUBK model and exposure inputs) should be assessed, as this will obviously affect model output. Use of NHANES data for water consumption: As stated in the draft report, there are no drinking water intake values specific to formula-fed infants in the NHANES data that are used in the SHEDS model; thus, the population that the NDWAC suggested for consideration is not considered in Approach 3. I understand that the NHANES data were used in order to ensure consistency between the IEUBK and SHEDS analyses; however, these data are quite different than those in the Exposure Factors Handbook (EFH). The EFH values should also be tested to examine how those affect model output. In addition to the water intake parameters, other parameter values used in this effort are different from those recommended by EPA for use in the IEUBK model and also different from those in the Exposure Factors Handbook. Although the draft report justifies use of values different from recommended values, EPA should consider the fact there should be consistency across the Agency when recommending parameters to be used for risk assessment purposes. As with the water intake parameters, the models should be run with the recommended/default parameters in order to examine how this affects model output. Model inputs should consider additional variability—i.e., in pharmacokinetic and metabolic parameters. The IEUBK model uses point estimates for model inputs; these inputs could be sampled from a distribution using a PBPK model combined with Monte Carlo analysis. I will defer to other experts on the panel who are more familiar with soil and dust ingestion rates and variability in lead water concentrations.
Nascarella	The input parameters for both the point estimate and distribution of water lead levels need further explanation. The report characterizes that public drinking water supplies are unlikely to have lead present at the source (p. 9), and water becomes contaminated due to the presence of lead pipes (i.e., lead service lines) or leaded plumbing parts (i.e., fixtures, solder, fittings). Given this characterization, when lead is measured in "first-draw" water, it is likely to be measured as a transient elevation, as a result of changes in water flow (i.e., particulate release or a bolus of stagnating water). Given this nature of lead release in drinking water supplies, it seems appropriate to present approaches to modeling the dose-response relationship that account for periods of acute exposure (24 hours or less), short-term exposure (1-30 days), and long-term exposure (more than 30 days).

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	The presented approaches do not seem to account for these conditions in either the exposure assessment or the characterization of the response. Additional effort should be made to characterize a level of lead exposure that accounts for this potentially sinusoidal pattern of exposure, and the resultant physiological impact of transient acute exposures to particulate-related spikes in Pb water concentrations, coupled with consistently elevated levels of lead (sometimes occurring simultaneously), as well as lead-free water. I found the section on Maternal Blood Lead (Section 5.10) confusing. The section begins by describing how the mean BLL for women of childbearing age was estimated using data from NHANES using the 2011-2012 and 2013-2014 survey years (n = 2,003). EPA pooled data files across the two survey cycles to create a 4-year dataset representative of the U.S. civilian, non-institutionalized population. The description of the age criteria for entry into this pool is written in a confusing manner, as it seems to imply that only parous women were included - i.e., "blood lead data were collected for all participants aged 1-11 years old." It is unclear why pooled analyses of women of childbearing age would consider the age of children. As regard to this specific parameter, the definition of women of childbearing age (i.e., 18-45 years) seems restrictive. I would suggest evaluating the sensitivity of this assumption to both a broader definition of "childbearing age" – to align with biological capability – perhaps begin at 15 years old (Johnson et al., 2006). I would also evaluate model estimates based on sensitivity to a parameter based on current trends, suggesting that mothers are typically older (CDC, 2017). These older individuals may have higher BLLs. The use of the IEUBK requires that the user specify a compartmental lead mass at "initiation" (simulated birth) for an exposed child. The model assumes that the blood lead concentration of this day 1 newborn child is 85% of the maternal blood lead concentration. This underscores the need for more details on the rationale to include a geometric mean BLL of 0.61 (SE = 1.02) µg/dL as default assumption on mother's blood lead concentration[2]. This seems very low, especially compared to the published geometric mean BLL of group such as Asians, reported as 1.15 µg/dL (NHANES, 2011-2012 survey years). It is noteworthy that the lower limit of detection (LLOD) in the NHANES data is different between the 2011-2012 and 2013-2014 survey years. For example, the LLOD for lead in blood in the 2011-2012 survey years is 0.25 ug/dL; compared to a LLOD for the 2013-2014 years of 0.07 ug/dL. This is a 3.5-fold decrease. Said differently, this is a 3.5-fold increase in the analytical ability to detect lead in a sample of blood. As regard to the approach for calculating aggregate results, if a measured value is below the limit of detection, the CDC analytic guidelines prescribe that you impute a value. For analytes with results below the LLOD, an imputed fill value equal to the LLOD divided by the square root of 2 (LLOD/sqrt[2]) is used (CDC, 2016). The clarification of this calculation

[2] Of note, Page 3 of the supplemental material in Zartarian et al. (In Press) manuscript describes an assumption of "maternal blood lead of 1 µg/dL". This too is confusing and I am unsure when the assumed maternal BLL being used is 0.61 and when it is 1.0.

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	should also describe how many blood lead measurements were actually available (N missing), and how this relates to the survey weights and representativeness of the U.S. population of women of childbearing age. As any of the EPA modeled approaches appear sensitive to this estimate, the sensitivity of the calculation of the new maternal blood lead calculation should be explored. It is unclear why the water consumption rate is based on NHANES data, and not more typical data such as the Exposure Factor Handbook or World Health Organization default data. It is also not clear to what extent EPA considered the alternative water model (IEUBK Equation E-6b; INWATER(t)). This value is calculated as the product of the water consumption rate, and a lead concentration that is calculated as a weighted average of the user-specified constant value as well as values from the home first-draw (FirstDrawConc), a flushed faucet at home (HomeFlushedConc), and a water fountain outside the home (FountainConc).
Ryan	I have some concerns about the model input data. My most serious concern is the lack of variability for dust and soil ingestion across age groups. I am fine with the 0-6-month age group having no soil/dust ingestion as their mobility is very limited. But the lack of variability in non-dietary intake is of concern for the older age groups. Why does it only vary by a few mg (out of 30 or so) across the 6-month to 7 year ages? Dietary lead is similarly fixed across age groups. Exhibit 6 - Drinking Water GSD. What do these numbers represent? The values - 0.0025, etc., do not have any correspondence with what is in the rest of the table. Please clarify. I reiterate - this must be fixed. This non-physical situation is a glaring error and must be addressed. Others mentioned this in pre-meeting comments and it was mentioned in brief discussion. It is not the most important part of our discussion, but is absolutely in need of modification. I think the selection of values, how they vary from the IEUBK default values, which is non-systematic, and my sense of reduced variability across life stages bears some discussion by the group. While a consensus is not needed in this type of review, I would like to hear arguments for and against the values selected. The discussion in the previous paragraph begs for an analysis of sensitivity in the model to variability in these parameters. I still find the fixed or minimally-varying parameters of concern. EPA should check all of these values again and certify that the best measures are being used and assess likely variability in intake parameters that may be seen in a reasonable population.
Vork	Comment: Can rate of breastfeeding among exclusively breast-fed infants be used as a surrogate for formula intake? There is a recent assessment of these rates that might be better than the sparse data (N=7) on rates of formula intake (Arcus-Arth et al., 2005).

Reviewer	Comments
	Arithmetic and geometric means have been selected for various parameters based on whether the data is "highly variable" or "due to the lognormal distribution of the input data". Have the "highly variable" datasets been examined for sources of heterogeneity?

1.3 MODELING APPROACHES

EPA demonstrated three modeling approaches. The first two are individual-based deterministic (with central tendencies) approaches using IEUBK modeling, and the third is a population-based probabilistic approach using SHEDS-Multimedia coupled with the IEUBK model. "Approach 1" determines the concentration of lead in drinking water associated with a percentage increase in the probability of an individual "representative" child experiencing an elevated BLL. "Approach 2" determines the concentration of lead in drinking water that would result in a 0.5 µg/dL or 1 µg/dL increase in a child's mean BLL for an individual "representative child" exposed to lead in drinking water. "Approach 3" determines drinking water lead concentrations that would keep particular percentiles of simulated national BLL distributions of different aged children below a defined benchmark BLL.

a) Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

b) Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.

c) Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

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Georgopoulos	The IEUBK User's Guide (2007) states, regarding the distribution calculated by the model, that "the plausible range reflects predicted variability among individuals with the same exposure scenario, and should not be confused with a statistical confidence limit (which is a measure of statistical uncertainty in a predicted value such as a geometric mean)" and that "the estimated probability of exceeding the specified PbB level of concern, corresponding to the given exposure scenario or scenarios (for multiple runs in a given medium)" can be interpreted in the following two ways: 1. The output of the model may be considered to be the best estimate of a plausible range of PbB concentrations for a hypothetical child under a specific Pb exposure scenario. The range of values is centered on the geometric mean PbB concentration expected for a typical child with this exposure scenario. The portion

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	of the upper tail of the probability distribution exceeding some chosen PbB level of concern provides an estimate of the risk of exceeding that level for a typical child of that age residing in the same household and with the same exposure history. 2. The output of the model may also be considered to be the predicted geometric mean PbB of a population of children under the same Pb exposure scenario. That portion of the upper tail that exceeds some chosen PbB level of concern indicates the fraction of the population exceeding that level when all of these children have the same exposure history. The IEUBK User's Guide (2007) also states that "[a] common misinterpretation of IEUBK is that it predicts community geometric mean PbB and the fraction of the population of children at risk when the input is the mean or geometric mean of household-specific environmental Pb concentrations. That misinterpretation arises, particularly when the environmental variables have a wide distribution among the neighborhoods of the community. A correct approach requires applying the model to each individual home (or area with homogeneous lead concentrations) and combining these results as an aggregate to form an estimate of neighborhood or community risk." Given the above statements, it can be claimed that the proper way of deriving a distribution of BLLs using IEUBK – and presenting the corresponding outputs, as per charge Question 3.a - is in fact the one provided by Approach 3. As mentioned in the responses to previous questions, Approaches 1 and 2 represent interesting case studies, but the results presented are not generalizable to any real population of concern. Approach 3 employs a probabilistic/distributional approach, implemented in a state-of-the-art exposure model, SHEDS. The document under review states (on p. 18), regarding SHEDS: "Several features of SHEDS contribute to making it a unique and powerful tool. First, since the model uses a time-series approach for simulating dietary and residential exposures, SHEDS accounts for variability that arises from separate activities or eating occasions. The model also uses two-stage Monte Carlo sampling, which allows variability in population exposure and dose estimates and uncertainty associated with different percentiles to be quantified. In addition, SHEDS-Multimedia can account for correlated inputs." The above statement is factually correct; however, it can be misleading in the context of the present effort, as not all mentioned features of SHEDS are used in the application currently under review. For example, two-stage Monte Carlo sampling is not used: only variability associated with exposure factors is explicitly considered via Monte Carlo; biological variability is "lumped" in the GSD used in conjunction with IEUBK (linked with SHEDS) and uncertainty is not treated. This is in fact discussed on p. 60 of the document under review: "uncertainties in this analysis are the model averaging time, and how the coupled models capture biological and other sources of variability in the geometric standard deviation of BLLs. The latter issue relates to model coupling for this analysis. SHEDS-Multimedia estimates reflect exposure variability, but not biological variability or other sources of variability such as measurement or model error. Because IEUBK blood lead estimates do not reflect inter-individual behavioral and pharmacokinetic differences, a GSD of 1.6 is applied to outputs of IEUBK to account for biological

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	variability and measurement error, but does not account for exposure variability. Outputs from the coupled SHEDS-IEUBK models, therefore, need a variability factor to account for the GSD difference between modeled and measured BLLs and reflect real-world BLLs that also account for biological variability." The use of this "extra" variability factor should be only considered an "interim solution" for the present application; it is strongly recommended that future work on the matter explores the feasibility of accounting for inter-individual variability via standard methods currently used in pharmacokinetic modeling practice such as Nonlinear Mixed Effects Modeling (NONMEM; see, e.g., Owen and Fiedler-Kelly, 2014; Wang, 2015). In any case, it should be noted that though SHEDS is a state-of-the-art probabilistic model, that has been continuously evolving and refined over the past two decades, IEUBK is a well-tested but now rather old tool (developed in the 1990s with data from the 1980s) that does not incorporate many recent developments in physiologically-based pharmacokinetic modeling and systems biology of exposures. It cannot account for episodic exposures (traditionally it has been applied for a minimum of 90 day periods over which exposures are taking place, though the current application considers 30 day exposures for the SHEDS-IEUBK simulation), it cannot account for changes in physiological parameters due to activity, etc. and it considers childhood life-stages in year-length periods. There are many factors that affect lead exposure biology that cannot be dealt with IEUBK. For example, co-exposures to other contaminants may affect prenatal and postnatal Pb toxicokinetics and toxicodynamics (see, e.g. Sasso et al. 2010; Boucher et al. 2014) while gender-related differences in exposure patterns and in the toxicokinetics of absorption, metabolism and excretion of Pb may account for gender-differences in Pb toxicodynamics and in Pb neurotoxicity (e.g. Mushak 2011; Senut et al. 2012; Vahter et al. 2007; Sen et al. 2015). In the future USEPA should consider either extensively updating IEUBK or adopting a PBPK formulation that extends, with variable temporal resolution over multiple lifestages and includes pregnancy/gestation with coupled mother/fetus models to account for *in utero* exposures. From a more short-term model implementation/coding perspective, an issue that should be addressed in the near future is the lack of flexibility in incorporating explicit input variability when using the "batch mode" of IEUBK (compared to the options available when using the "standard mode" of IEUBK, via the guided user interface windows, as discussed on p. 59 of the document under review. Implementing a more flexible "batch mode" could facilitate the "direct" coupling of SHEDS with IEUBK (i.e. instead of using a regression fit of IEUBK outputs) and even performing stand-alone (probabilistic) Monte Carlo applications of IEUBK. The current application utilized a polynomial regression fit of IEUBK solutions as a "fast equivalent operating model (FEOM)" closely approximating numerical IEUBK solutions via an algebraic formula. (Nevertheless, the exact range of applicability of any such "FEOM" must be explicitly identified and documented, in order to avoid any potential future "misuse" of the formulation outside this range.) Regarding Question 3.c, this reviewer would strongly recommend to use Approach 3 directly (instead of using it to address the questions of Approaches 1 and 2).

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Goodrum	In this report, EPA uses the term "probabilistic" in a manner that is likely to be confusing to many lead risk assessment practitioners who have experience using IEUBK and ALM. For many years, EPA has previously characterized the IEUBK and ALM models as probabilistic models because the output is a probability distribution of predicted BLLs for various age groups. With IEUBK and ALM, variability is not propagated throughout the model equations using a technique such as Monte Carlo analysis (MCA). However, risk metrics are still expressed in terms of the probability of exceedance of BLRVs. I also believe it may be confusing to categorize Approaches A and B as "individual-based", whereas Approach 3 is "population-based". Certainly the IEUBK model, run in a standard mode with recommended default inputs, has a long track record of assisting with risk management decisions directed at protecting populations and, in fact, is specifically not intended to be used to assess risk to an individual. I think this Charge Question is trying to highlight how Approach 3 is different because it explicitly models the multiple exposure pathways that are potentially contributing to exposure and BLLs for children throughout the U.S. Furthermore, variability in lead concentrations in various exposure media likely contribute to the distributions of BLLs observed in NHANES, so it makes sense to try to capture that source of variability also. But there's a simpler way to achieve this objective by using the IEUBK model coupled with a more direct use of the NHANES dataset – we'll call that "Approach 2.5", as my colleagues on the peer review panel suggested, and it is discussed below. **a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.** In terms of risk metrics, EPA may want to consider a hybrid of Approach 1 and 3, whereby a health-based benchmark achieves two objectives: 1) limit the delta (change in BLL at some upper percentile of the distribution); and 2) limit the percentile value so that the probability of exceeding a BLRV is constrained to a small value. The latter is a more familiar risk metric for IEUBK model users – many are familiar with the former "P10" statistic, whereby the goal was to identify a media concentration (usually lead in soil) that limits the probability of BLL greater than 10 µg/dL to 5 percent. Likewise, the former "delta method" is a familiar risk metric in prominent national programs involving risk management of lead, including the National Ambient Air Quality Criteria for lead and the Lead Renovation, Repair, and Painting Rules. The delta method is also used in applications of California's Leadspread model (California EPA 2016). Strengths of both the delta BLL and the upper percentile (absolute) BLL is that they can be related directly to epidemiologic studies and CDC recommendations regarding BLRVs. Approach 2 relies on a delta in the GM BLL. This approach can be evaluated without needing to impose a GSD assumption (as in Approach 1), or run a series of Monte Carlo simulations (as in Approach 3). So while it is relatively simple to implement and is not sensitive to uncertainty in methods used to quantify variance, it is unclear what the (health) basis is for a delta GM of 0.5 µg/dL or 1.0 µg/dL.

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	b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs. The IEUBK model is an appropriate tool to evaluate a range of drinking water exposure scenarios. A major strength of IEUBK is that the model is easy to use, relatively simple to summarize, and model runs are readily reproduced. It can evaluate each of the risk metrics specified in the Report, including the Approach 3 metric involving exceedance probabilities of BLRVs. The IEUBK model limits the average time for input variables to one-year increments. Therefore, it is more challenging to evaluate scenarios that involve short-term exposures (i.e., less than 1 year, but at least 3 months). However, as discussed below (comments on Charge Question 5), EPA's guidance on intermittent exposures as well as several published examples in the literature illustrate how this can be done. **"Approach 2.5"** Another strength of the IEUBK model is that it can be used to specify baseline conditions without having to model all exposure pathways. In a sense, it can be run in a "paired down" mode whereby all of the non-drinking water pathways are shut off, and replaced by the "Alternate Exposure" menu. This menu accommodates age-specific inputs of average daily intake, which can easily be converted to uptake by specifying an Absorption Fraction of 100%. An example of this is given below for the 1-2 year age group, using the input values specified in the Report to facilitate comparisons. The concept of building in additional pathway after having established baseline conditions (BLLs) has been used previously by EPA and published by Maddaloni et al. (2005). **Steps for Approach 2.5** 1. Establish baseline using "Alternate Lead Intake" menu and zeroing out all other pathways. 2. Set maternal PbB to 0.61 µg/dL, per Section 5.10 (based on NHANES 2011-12 and 2013-14, pooled to create a 4-yr dataset for women ages 28-45 years, N=2,003). 3. Change the intake rate (µg/day) for 1-year age groups until the GM PbB for the age group of interest matches NHANES. For simplicity, set AF = 100% for alternate pathway. 4. Run IEUBK and select the option to display results as text (rather than graphics). Note what the corresponding uptake rate is for each age group (also in units of µg/day); even though AF=100%, uptake is slightly lower than intake due to nonlinearities in the uptake module. 5. Run IEUBK and select the option to display graphics. Only this display of results will show GM to 3 significant figures. 6. Match the GM PbB to 3 significant figures for NHANES age groups (add an extra zero to Table 1 of Zartarian et al. 2017): Age Group | N | GM BLL (µg/dL)

Reviewer	Comments

1 to < 2 yrs	475	1.16	>> add extra zero when matching with IEUBK: 1.160
2 to < 6 yrs	1,892	1.03	>> add extra zero when matching with IEUBK: 1.030

7. Assign baseline for each of 3 age group scenarios, noted below.

Age Group	GM BLL (µg/dL)	Notes
0 to 0.5 years (0 to 6 months)	1.160	Since NHANES does not report BLLs for < 1 year, this is an assumption.
1 to 2 years (24 to 48 months)	1.160	GM BLL for age group, matches the same age group noted above
0 to 7 years (0 to 84 months)	1.030	GM BLL for age group, assumed to be well estimated by 2 to < 6 yrs given above

8. Now add in a Water Ingestion scenario, using prescribed water ingestion rates from Report Exhibit 6, plus extra scenario for 0-6 month formula-fed population (Appendix A).

Age Group	N	GM (L/day)	
0-6 months	1,246	0.526	>> from Exhibit 6, based on NHANES 2005-2011. Use this for 0-1 year age group as input to IEUBK
0-6 months	346	0.640	>> based on USDA CSFII 1994-96 and 1998, as analyzed by Khan et al. (2013, Table 2b). Use this for 0-1 year age group as input to IEUBK
0-1 years	2,618	0.410	>> from Exhibit 6, based on NHANES 2005-2011 (for all remaining age groups). Use this for both 1-2 year and 0-7 year scenarios.
1-2 years	1,792	0.151	
2-3 years	1,848	0.176	
3-4 years	1,272	0.193	
4-5 years	1,358	0.197	
5-6 years	1,196	0.213	
6-7 years	1,306	0.228	

Table 3 below gives the results following these steps. Figure 1 is based on the information presented in the table. Note that the relationship between concentration in water and GM BLL is linear. The intercept (when concentration in water is zero) corresponds with the GM BLL reported for NHANES 2005-2011.

Reviewer	Comments
	It is clear that similar graphics could be generated for other age groups relatively easily by running perhaps 3 to 5 different concentration in water to derive the linear relationship. Once the GM BLL is estimated,

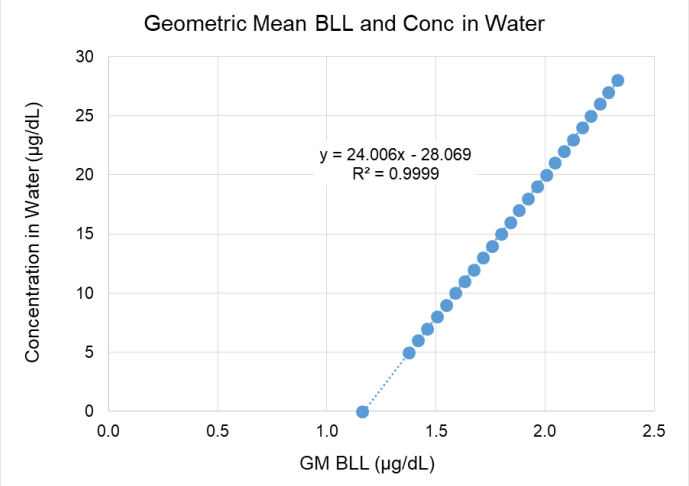

Figure 1. Example of relationship between GM BLL and lead concentration in water for ages 1-2 years.

Table 3. Example of "Approach 4" used to combine alternate (to reproduce NHANES BLLs) and drinking water exposure pathway.

Water	Uptake (µg/day)			GM BLL	P(BLL>x)	
µg/L	Water	Alternate	Total	µg/dL	3.5 µg/dL	5.0 µg/dL
0	0.000	2.599	2.599	1.160	0.938	0.094
5	0.368	2.591	2.958	1.375	2.341	0.301
6	0.441	2.589	3.030	1.418	2.725	0.366
7	0.514	2.587	3.102	1.460	3.146	0.441
8	0.588	2.586	3.173	1.503	3.603	0.527
9	0.661	2.584	3.245	1.545	4.097	0.624
10	0.734	2.582	3.316	1.587	4.627	0.732
11	0.806	2.581	3.387	1.630	5.193	0.853
12	0.879	2.579	3.458	1.672	5.795	0.987
13	0.952	2.578	3.529	1.714	6.432	1.135
14	1.024	2.576	3.600	1.755	7.103	1.297
15	1.097	2.574	3.671	1.797	7.807	1.474
16	1.169	2.573	3.742	1.839	8.543	1.665
17	1.242	2.571	3.813	1.880	9.309	1.872
18	1.314	2.570	3.883	1.922	10.105	2.095
19	1.386	2.568	3.954	1.963	10.928	2.334

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20	1.458	2.566	4.024	2.004	11.778	2.588
21	1.530	2.565	4.095	2.045	12.652	2.859
22	1.602	2.563	4.165	2.086	13.550	3.147
23	1.674	2.562	4.235	2.127	14.469	3.450
24	1.745	2.560	4.305	2.168	15.408	3.771
25	1.817	2.559	4.375	2.209	16.366	4.107
26	1.888	2.557	4.445	2.249	17.341	4.460
27	1.960	2.555	4.515	2.290	18.331	4.829
28	2.031	2.554	4.585	2.330	19.335	5.214

Now each of the risk metrics can be solved for the concentration in water (Conc W).

Risk metric from Approach 1, using GSD = 1.6 and 1.9.

Approach 1

Baseline					Add 1%		Add 5%	
GM	GSD	>3.5	A = P(BLL > 3.5)	B = P(BLL > 5.0)	A + 0.01	B + 0.01	A + 0.05	B + 0.05
1.160	1.6	0.00940	0.00940	0.00094	0.019396	0.0109401	0.059396	0.05094

p	z(p)	BLL	GSD	GM	Conc W	
0.980604407	2.066	3.5	1.6	1.325	3.7	change of 1% exceedance of 3.5
0.940604407	1.560	3.5	1.6	1.681	12.3	change of 5% exceedance of 3.5
0.98905988	2.292	5.0	1.6	1.702	12.8	change of 1% exceedance of 5
0.94905988	1.636	5.0	1.6	2.318	27.6	change of 5% exceedance of 5

Sensitivity to GSD

Baseline					Add 1%		Add 5%	
GM	GSD	>3.5	A = P(BLL > 3.5)	B = P(BLL > 5.0)	A + 0.01	B + 0.01	A + 0.05	B + 0.05
1.160	1.9	0.04267	0.04267	0.01142	0.052666	0.0214156	0.092666	0.061416

p	z(p)	BLL	GSD	GM	Conc W	
0.947333922	1.620	3.5	1.9	1.238	1.6	change of 1% exceedance of 3.5
0.907333922	1.325	3.5	1.9	1.496	7.8	change of 5% exceedance of 3.5
0.978584381	2.025	5.0	1.9	1.363	4.6	change of 1% exceedance of 5
0.938584381	1.543	5.0	1.9	1.857	16.5	change of 5% exceedance of 5

Risk metric from Approach 2:

Approach 2

GM_baseline	+ Delta	GM	Conc W
1.160	0.5	1.660	11.8
1.160	1.0	2.160	23.8
Note: GSD is not needed for this approach			

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<tr><th>Reviewer</th><th>Comments</th></tr>
<tr><td></td><td>
Risk metric from Approach 3, using GSD = 1.6 and 1.9:

Approach 3

<table>
<tr><th>p</th><th>z(p)</th><th>F(x)</th><th>GSD</th><th>GM</th><th>Conc W</th></tr>
<tr><td>0.975</td><td>1.960</td><td>3.5</td><td>1.6</td><td>1.393</td><td>5.4</td></tr>
<tr><td>0.95</td><td>1.645</td><td>3.5</td><td>1.6</td><td>1.616</td><td>10.7</td></tr>
<tr><td>0.975</td><td>1.960</td><td>5.00</td><td>1.6</td><td>1.990</td><td>19.7</td></tr>
<tr><td>0.95</td><td>1.645</td><td>5.00</td><td>1.6</td><td>2.308</td><td>27.3</td></tr>
<tr><th>p</th><th>z(p)</th><th>F(x)</th><th>GSD</th><th>GM</th><th>Conc W</th></tr>
<tr><td>0.975</td><td>1.960</td><td>3.5</td><td>1.9</td><td>0.995</td><td>-4.2</td></tr>
<tr><td>0.95</td><td>1.645</td><td>3.5</td><td>1.9</td><td>1.218</td><td>1.2</td></tr>
<tr><td>0.975</td><td>1.960</td><td>5.00</td><td>1.9</td><td>1.421</td><td>6.0</td></tr>
<tr><td>0.95</td><td>1.645</td><td>5.00</td><td>1.9</td><td>1.740</td><td>13.7</td></tr>
</table>

c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).

Clearly the SHEDS-IEUBK approach can be used to evaluate the risk metrics specified in both Approach 1 and 2. However, as shown above (Approach 2.5) and previously discussed, the SHEDS-IEUBK approach introduces several sources of uncertainty. These uncertainties are not necessary given the nature of the charge question.
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<tr><td>von Lindern</td><td>
a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.

AS EPA notes, Approaches 1 and 2 apply the same model to project outcome blood lead levels. Both approaches develop the same baseline blood lead distribution resulting from sources other than water. Approaches 1 and 2 differ only in how the results are presented. Both methods determine a baseline blood lead level from other sources and then add water lead increments to the model to effect blood increases. As noted above, manipulations made to the IEUBK input likely yield spurious baseline results for the purpose of health risk assessment; but with appropriate inputs the methodology is sound. Approach 1 focuses on the tail of the response generated from the distributional module and identifies water lead concentration that increase the probabilities of exceeding the EBLLs by 1% and 5%. The result can be interpreted as the incremental probability that an individual child will exceed the threshold level due to the water lead source, or the number (or percentage) of children whose blood lead levels will increase above the threshold. Because these predictions occur in the tail of the distribution,
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	there is less certainty than the prediction of changes in the mean in Approach 2. The utility of the result is that EPA could develop a "benchmark policy" defining unacceptable risk in terms of the probability of exceeding a health threshold. The public health official, parent, or school superintendent who receives this notice would be hard-pressed to interpret this in practical terms, other than to say EPA thinks it is too high. In reality, the 1% or 5% increase due to water lead implies these children move from slightly below the threshold to slightly above the threshold, not from safe to unsafe. An important question for EPA is how the threshold is defined. Approach 1 has the additional problem in the current report that input of geometric mean ingestion rate estimates for soil and dust based on a logarithmic distribution with a gsd>3, diminishes the validity of the 1.6 gsd used to calculate percentile values in the distribution module of the IEUBK (See Response to Question 3c). As a result, the water lead levels estimated in the current report were derived from the tail of the distribution and are likely doubly unreliable for health risk assessment purposes. In Approach 2, candidate benchmark water concentrations are derived from baseline geometric mean BLLs, by determining the water lead increment that would increase the mean by 0.5 µg/dL or 1.0 µg/dL. This methodology is also sound, but with the caveat that the means were calculated inappropriately, as noted above. This calculation has more certainty as it is performed at the central tendency of the distribution. The results can be interpreted as the increase in blood lead level the typical child will experience from drinking this water, and there is a particular loss of IQ that can be related to the blood lead increment, again for the typical child. However, the child with the mean, or most likely or typical, response is not the most at-risk. The larger concern is with the children in the upper tail of the distribution who will have a greater baseline value and incremental response. That response and total lead level, however, can be calculated from the mean at any percentile of the population; and can be related to potential IQ loss, as well. For example, the benchmark notice could be transmitted with the interpretation that the typical child would experience a 1.0ug/dL increase, with some children as much as 2.0ug/dL. This interpretation seems easier to comprehend and more practical for the parents, school officials and water systems authorities that receive the benchmark notice (e.g., your child is likely to lose 1 or 2 IQ points from drinking this water). However, in the interests of openness and transparency, there remains the problem that these effects are incremental to the baseline for both blood lead and IQ. The baseline also has associated risks of adverse health effect risks. In most affluent, rural and newer suburban communities the baseline blood lead levels are low; but the bulk of the overall effects are associated with mainly the water lead increment. In already exposed communities, the water lead should be interpreted as increasing ongoing adverse effects and further depressing IQ. As an alternative Approach to better assess and convey both these risks, the models could be run for a series of baseline blood lead levels. The results of Approaches 1 and 2 could be combined in age-group specific matrices with columns indicating incremental water lead concentrations and rows indicating baseline blood lead means. The matrix cells for Approach 1 would contain %-tiles to exceed EBLLs. These %-tiles could be

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	interpreted to represent the probability a child from that background environment would exceed the EBLL level. EPA could then stratify the national exposure profile and develop aggregate background BLL representing exposure indices for US communities (e.g., post-1970 suburban communities, rural, mid-sized cities, inner city low quality housing, etc.). The potential effectiveness of water concentration levels could then be evaluated in terms of effectiveness in moving children below threshold values and exposure profiles (or communities) where the target EBLLs cannot be achieved. Similar matrices could be developed for Approach 2 indicating predicted blood lead increments at select distribution %-tiles (e.g., 50, 95, 97.5). A zero-background blood level could be included to evaluate the impact of water alone. These analyses pre-suppose that appropriate inputs are made to the IEUBK. This would include modifying the ingestion rate values and developing more representative soil and dust concentration partitions for the stratified exposure scenarios. EPA also asserts that population wide-estimates of relative source contributions available from the SHEDS output cannot be accomplished with the IEUBK. The IEUBK does provide relative contributions for a population of similarly exposed children. Estimates of relative contributions for the national population could be obtained by aggregating IEUBK runs stratified for the US population. This would be an amplification of the IEUBK application for children in homes with lead paint in Appendix B. That is, a series of defined exposure stratification scenarios that encompass the US population that could be aggregated proportional to population. Comparisons to SHEDS or NHANES could then be made to aggregations of the stratified Approach 1 results. Or, the SHEDS output could be used to inform the exposure stratification scenarios to be developed as case histories by the IEUBK. In Approach 3, EPA developed a national baseline distribution of daily lead exposure in µg/day from probabilistic background (all sources other than water) lead concentrations and children's activity patterns. Water lead was then added to determine the concentrations that could keep blood lead levels at specified percentiles of the simulated U.S. childhood population below specified "targets." Approach 3 results are useful in assessing the national implications of drinking water lead levels, in relation to the overall lead exposure distribution and current baseline blood lead levels. These results could be used to evaluate the number of children nationwide that might be affected from implementation of various benchmark levels. However, it does not help in evaluating the effectiveness of the "target" level, other than identifying the percentage of children nationwide that cannot be brought under the threshold, even at zero water lead. (See the historical discussion of the "target level in Response to Question 3c). EPA notes the ability to evaluate the contribution of all exposure pathways to BLL across the distribution of BLLs and asserts that population-based approaches allow a better characterization of variability in physiology and exposure than those based on a modeled individual, which EPA suggests is not possible with the IEUBK. These assertions require some qualification. Approach 3 estimates the contribution to total absorption by pathway for the aggregate US population (as represented by NHANES); but that applies to children in total across the population and national exposure profile. Although this is of considerable use in assessing the national implications of implementing health protective

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	policies, these results can only be interpreted as "somewhere in this country this number of children are suffering lead poisoning and reducing their drinking water exposure will provide relief to some number of them." In addition, EPA notes "population- based approaches are consistent with previous EPA methods for assessing lead exposures." Of course, in order to do so, EPA will have to determine what blood lead level constitutes lead poisoning (or accept CDC's definition), what percentage of the population over that threshold is excessive, and how to mitigate risk for those children (See Response to Question 3c). **b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.** A primary strength of the IEUBK model is that it does predict blood lead and probability increases associated with exposure increments to baseline exposure scenarios reflecting other sources in children's environments; and it does indicate the relative route-specific intakes, uptakes, and contribution to blood lead. As a result, risk management decisions can be based on both incremental and total risks. It is possible to convey to parents, school officials and public health practitioners both the incremental effects of contaminated water and the potential for overall lead health damage in their communities, as opposed to the entire country. That is, provided the community baseline is known. The IEUBK has the distinct advantage that it can be applied to particular baseline situations and provide site-specific (or scenario-specific) results, as demonstrated in Appendix B. The output from these site-specific or representative community scenarios can be used to determine the "target" percentile in those communities where media-specific regulation becomes ineffective in keeping children below health criteria. The principal weakness in IEUBK applications is predicting the blood lead response to short-term spikes in exposure, or a series of spikes, as the IEUBK kinetics assume steady- state exposures over a lifetime. However, relatively little is known as to the actual effects of these exposures, so this represents a gap in knowledge regarding lead poisoning response, as well as the inability to model the same mathematically, as is the case with most environmental contaminants. The report would benefit from a more extensive description of the variability of lead concentrations in the more at-risk water systems, particularly with regard to the extreme short-term spikes in concentrations related to physical, chemical, or water quality changes. The IEUBK operates in the chronic to sub-chronic exposure and disease spectra; whereas the exposures of concern in many of these events might be considered sub-acute and other assessment, modeling, or response strategies might be considered. **c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated**

	with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK). Overall, the use of the SHEDS model to estimate increments in geometric means or percentage to exceed threshold concentrations in the tail of the distributions brings up several questions with respect to its utility in developing and employing a benchmark health standard. A most fundamental consideration is evidenced by the many comments elicited by the SHEDS application. Most of the effort in Approach 3 is directed at trying to develop a national distribution of lead intake using scores of variables and distributions. This expansive undertaking is, doubtless, a valuable research exercise that should be pursued and will likely become an important tool in assessment of the national health picture with respect to numerous contaminants and exposure pathways. In this application, however, most of the attention has been diverted to critique of the input variables and notable weaknesses related to variable constructs, correlations, truncation, appropriateness of catch-all variance assumptions etc., and not on the health implications implied by the outcome blood lead levels. The use of a simple blood lead level platform (baseline blood lead levels related to US communities) might be more utilitarian in conveying the potential implications of contaminated water in a particular US community. With respect to estimating changes in geometric mean levels, the health significance of the geometric mean blood lead level of the exposed population is difficult to convey. What exactly does a change of 1ug/dl in the geometric mean of the country with a large gsd imply, particularly when discussing the problem in a local school? Moreover, the health significance of a 1% change in the probability of exceeding a 97.5%-tile blood lead levels is even more difficult to grasp when applied to an immense population that is largely unaffected. This becomes even more confusing given that the method to determine the benchmark level was developed using the observed baseline US water lead distribution and then substituting a point water lead concentration, as opposed to a truncation of the original distribution. This seems to imply in practical terms, that the latter scenario assumes all the nation's children are subjected to the target concentration. Does this mean the risk communicators' message would be "if all the children in the US had to drink this water, the result would be XXX many more poisoned children." In developing this health criteria, EPA should recognize that the public health representatives will need to convey not only the risk but also EPA's thinking and methodologies that go into the determination and meaning of the criteria. Since the early days of IEUBK analyses in the Superfund Program, various researchers have advocated developing a probabilistic front-end exposure module for the IEUBK model. Although there has been broad support for continuing to develop these modules for research and academic purposes, this approach, historically, has been rejected as a regulatory tool for a number of reasons. Most criticisms cited the large uncertainties and lack of support data associated with developing distribution variables for the numerous inputs, inherent problems associated with truncation and correlation among the many input distribution variables noted by some public commenters, and the enhanced "opportunity for mischief" by those inclined to manipulate the results. The development of the SHEDS models and publications have notably advanced the development of such probabilistic tools; and EPA has used the model to support risk assessment analyses for other toxins, as noted. However as

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	acknowledged by EPA, Approach 3 does not actually develop a probabilistic front-end exposure module for input to the IEUBK. Rather, Approach 3 might be better described as developing a surrogate biokinetic regression formula emulating IEUBK blood lead predictions as a back-end to the SHEDS exposure model. In attempting to compare the performance of the two models, the inputs to the IEUBK were inappropriately modified to reflect the inherent assumptions of the SHEDS Approach 3, as noted in detail above in response to Question 2. It seems the most substantial difference in the SHEDS and typical IEUBK analyses is the substitute use of geometric means derived from SHEDS analyses to characterize input values in the IEUBK, reportedly done for comparative purposes. There is little doubt, this greatly changes the predicted blood lead distributions that would otherwise be obtained from the IEUBK model. Although the differences in the diet component should be further examined and discussed, the critical differences are soil/dust ingestion rate, soil/dust lead concentration, and drinking water intake. The current combination of these values input to the IEUBK likely yields spurious results that have little health relevance. This leaves open the question of the health relevance of the SHEDS model results, as it uses the same inputs and yields similar results. EPA notes in interpreting IEUBK model results: "In considering these "individual" approaches, it is important to recall that the output of the IEUBK model may be interpreted as being representative of an individual, or of a group of individuals with identical exposure profiles. The geometric mean BLL represents a singular estimate for the BLL of an individual or identical group, while the BLL distribution represents the range of plausible BLL values and provides the probability of a child or group of children having a BLL above a specified value." While one might consider changing "identical" to "similarly exposed" and "singular estimate" to "typical or most likely", it is most important to remember that these applications assume logarithmic distributions of the predicted outcome blood lead levels that reflect the nature of the blood lead distribution in observed populations. The distribution of plausible blood lead response is generally characterized by the gsd. There has been considerable debate over the years as to what gsd value should be applied and what it represents. Values as low as 1.4-1.5 have been observed among infants with single exposure source, as noted in this report, and among heavily exposed populations in smelter communities and urban neighborhoods with extremely high blood lead levels in the 1970s. Some populations evaluated with the IEUBK model at hazardous waste sites showed gsd values near 2.0, and EPA has settled on a value of 1.6 in most applications large as an empirical compromise, that anticipates an arithmetic mean ingestion rate. Because there are few "identically" exposed populations, the 1.6 gsd likely reflects both individual variation across the bio-kinetic responses and measurement error, plus some inherent variation in the exposure variables (i.e., the difference between "identical" and "similarly exposed", which does not fit the classical definition of measurement error).

Reviewer	Comments
	EPA elected to use geometric mean of 26.6mg/day for all ages and apply a large gsd (3.3?) in Approach 3 to account for the variance in the US population, and applied the same geometric mean value as a point ingestion rate in Approaches 1 and 2, subsequently depending on the 1.6 gsd applied in the following step to account for any variation. The use of the geometric mean likely makes the 1.6 gsd inappropriate, and the resulting blood lead predictions spurious. Although the details of the methodology to calculate 26.6mg/day are not included in the report and don't seem to be apparent in reviewing Ozkaynak et al. (2011), it is assumed that the mean and the probabilistic distribution applied is related to the log normal fit to the model output referenced in Ozkaynak et al. (2011) (35.7mg/day,3.3gsd). The same study shows an arithmetic mean and 95th %tile ingestion rate (68 and 224 mg/day, respectively) similar to other studies, but lower than the EPA Exposure Factors Handbook suggested 100 mg/day default recommendations. EPA assumed the over-predictions by default inputs to the IEUBK are due to overestimation of the ingestion rates. Although this over-prediction of NHANES blood lead levels could, in part, be due to some overestimation of the ingestion rate, it also may result from the simplistic point estimates of soil/dust concentrations that fail to capture the variance in US soil/dust exposures. The model used to develop the input ingestion rate distribution for Approach 3 includes 20 variables, with 8 distribution forms, and 3 levels of confidence in the supporting data. It is not unexpected that a multiplicative model with these many variables, and some with low levels of support data, would produce large gsds and lower geometric means than indicated in observational studies. Sensitivity analyses conducted in Ozkaynak et al. (2011) show dust loading on carpets, soil skin adherence on hands, number of hand washes/day, and %-floor cover by carpets as the most sensitive variables. The reliability of the distributions of these variables nationally is of some question. Appling the geometric means of national population exposure variable distributions developed in Approach 3 to the IEUBK encompasses large variation in several sources, co-factors, and exposure profiles that likely bring the application of the 1.6 gsd into question. This implies that half of 2-year-old children in the US have ingestion rates lower than 30mg/day, at most scaled up to 80mg/day at +2gsd when applied in the IEUBK. These lower geometric means and high gsd values used by EPA in this report are consistent with some tracer studies as noted in Ozkaynak et al. (2011). It should be noted, however, that the large variation in tracer studies has been a subject of debate for some time and results in ingestion rates that differ substantially from those determined by other methods and those employed in other EPA regulatory applications. Use of these ingestion rates would constitute a major change from current EPA policy in other programs. Moreover, those most sensitive variables noted in the model-generated ingestion estimates are home and personal hygiene, behavioral, and socio-economic related factors. When combined with the large gsd, those variables could be interpreted as suggesting that lead poisoning problems in the US are confined to a small percentage of the population in extremely dirty homes, with poor housekeeping, hand washing, and bathing practices; while the vast majority of children ingest less soil and dust than previously assumed in regulatory analyses. This could continue to fuel, or reignite, arguments that childhood lead poisoning is a parental and child behavioral problem,

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	rather than a pollution problem. This argument has largely been refuted by the dramatic decrease in BLLs in children in the US achieved through regulatory actions to reduce lead pollution in their environment. With regard to Approach 1, or estimating threshold values from the tail of the blood lead distribution, EPA is attempting to apply the IEUBK across the NHANES populations that exhibit much greater gsds, that challenge the assumption of similarly exposed population groups. EPA has, in effect, diluted the tail of the distribution as NHANES purportedly represents tens of millions of children with little or no significant drinking water (or total) exposure in the analyses. This makes the 95% and 97.5%-tile targets arbitrary percentages largely determined by the size of the overall population, rather than identifying those whose risks may not be sufficiently addressed through the standards determined from the central tendency. From a public health perspective, the emphasis should not be on the tens of millions who are safe, but on the hundreds of thousands of children at risk. It is possible that these at-risk children are not found in the tail of a national logarithmic distribution; but may be in a bi-modal distribution, where most US children are protected, and a minority are experiencing different "similarly exposed" scenarios. The pertinent question is how many of these at-risk children can be efficiently protected by lowering the media concentration limit (or some alternate form of household health-based benchmark), or is their exposure due to factors that require additional protective measures? The evaluation of the entire US population as a single distribution may serve to provide perspective on the overall level of protectiveness and residual risk in public water systems; but it provides little assistance in evaluating the efficacy of health-related benchmarks. EPA should consider stratifying the national data bases into similarly exposed sub-groups and analyzing the data with respect to more representative upper limits. Regarding Approach 2, or calculation of benchmark water concentrations from predicted mean blood lead levels, the report does make comparisons between the predictions of the surrogate IEUBK regression and IEUBK model runs inputting the same absorbed lead into the "Other" intake route of the IEUBK, noting less than 5% differences in results. This result would be expected, but as EPA noted, this occurs after the exposure and absorption modules of the IEUBK and is simply the absorbed lead intake feed to the bio-kinetic module. The regression is similar to the biokinetic module used in the earliest forms of the IEUBK. That was a linear application of the Harley-Kneip (HK) coefficients obtained from controlled absorbed lead dosage of juvenile baboons. The following Table compares the surrogate regression Beta (1) and HK coefficients: **Comparison of IEUBK Surrogate β1 to Original HK Coefficients** Age Interval — Exhibit 36. β1 Value — H-K Coeff. 0.5-1 — 0.547 — - - 1-2 — 0.447 — 0.297

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	2-3 0.379 0.404 3-4 0.355 0.366 4-5 0.336 0.350 5-6 0.313 0.363 6-7 0.288 0.345 The surrogate analyses showed a .995 R-square correlation with IEUBK model runs using the alternate source route, and likely indicates that substitute regression equation accurately predicts the IEUBK biokinetic calculations. However, two questions arise. As EPA notes, the exposure route and absorption components of the IEUBK are not included, limiting the route-specific options in the model. One concern is with respect to use of the "Other" route to evaluate the efficacy of this surrogate method. As EPA notes, use of the alternate pathway option in the IEUBK fixes lead intake over the life of the child, and bypasses the IEUBK capability to assess age-specific exposure considerations. These analyses could be greatly improved by actually developing a probabilistic front-end to the IEUBK providing age and route-specific intakes determined from stratified soil/dust ingestion and concentration partitions input in batch mode. A second concern is with the disparity in the absorbed lead and blood lead coefficients in the above table for the youngest children. Although, the IEUBK itself may produce the same results, the surrogate coefficients for 1-2-year-old children are much higher than that observed in the original primate studies, and there were no observed data for infants. EPA's modifications for the youngest age group, in both the IEUBK and SHEDS model surrogate equation shows the highest coefficients and would yield the highest blood lead levels for these children. The blood lead predictions for these children are based on EPA theoretical adjustments made to the IEUBK and are substantially higher than H_K observations. Because this age band is a critical population, EPA should acknowledge and discuss the experience, support material, and reliability of the results for this age group in contrast to older children. One interesting SHEDS findings was that no level of water lead would bring the population below the 97.5% target EBLLs. This should not be regarded as an artifact of the analyses. There are significant numbers of children in the US above these levels due to sources other than water. That Approaches 1 and 2 did not predict these children is, likely, an indicator that the baseline blood lead levels are under-predicted. Some children in the 95th plus percentiles should be predicted by the IEUBK using the 1.6 gsd. These children not showing up in these analyses is an indicator that the baseline estimate is too low; or that the contemporaneous effect of water lead is greater, and would be further underestimated by the reduced consumption rates adopted by EPA in these analyses.
Loccisano	I understand that the IEUBK model is EPA's standard approach to lead modeling in children, it has been through peer review, and that revisions have been made based on recommendations from review panels. The strength of the IEUBK model is that it is easy

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	to use; however, since the IEUBK uses point estimates as input parameters, variability is not accounted for here, but rather variability is accounted for by use of the GSD (1.6) for BLLs. A potential useful (alternative) approach to use of the IEUBK model would be the use of a physiologically-based pharmacokinetic model, such as the O'Flaherty lead model[3], which is capable of examining BLLs associated with different exposure sources. Use of this model would permit a Monte Carlo approach, where variability in both biological parameters (physiology and pharmacokinetics) and exposure parameters could be varied during different life stages (while accounting for correlations between variables). This would allow for the examination of variability in BLLs resulting from differences in physiology and exposure. This would also allow for examination of the contribution of various exposure sources to BLLs. The SHEDS model could also be coupled with the PBPK model (as has been done with permethrin and arsenic).[4] Approach 3 seems to be the best out of the 3; this is a probabilistic approach and is thus more scientifically sound and seems to be in line with how EPA approaches probabilistic risk assessment in other areas (e.g., pesticides). However, a more straightforward approach would be to directly link the IEUBK and SHEDS models rather than use of regression equations. If the regression approach is used, this should be justified and explained more clearly.
Nascarella	The IEUBK model is supported by US EPA guidance that specifically states that the model should not be used for (a) exposure periods of less than three months or when (b) high exposure occurs less than one per week or varies irregularly. This is fundamental to the use of this model, as the IEUBK is based on a central premise that steady-state exposure can be understood through movement of environmental lead, mediated by a blood/plasma compartment. The IEUBK is essentially a model of plasma exchange, with the long-term lead-binding constituents of the skeleton. In fact, the IEUBK Model has been designed and validated to model the physiological effects of lead over relatively steady-state exposure conditions (i.e., chronic exposure). The EPA application in the subject document does not seem to be consistent with this application. The nature of lead release in drinking water supplies is so highly variable that it presents acute, short-term, and long-term exposure conditions – in addition to true chronic conditions. EPA should describe how the approaches constitute a steady-state exposure condition, consistent with the application of this model. This is fundamental to the use of this model, as the IEUBK is based on a central premise that steady-state exposure can be understood through movement of environmental lead, mediated by a blood/

[3] O'Flaherty, EJ 1998. A physiologically based kinetic model for lead in children and adults. Environ Health Perspec, 106 (Suppl), 1495-1503.

[4] Toxicol Sci. 2012 Nov;130(1):33-47. doi: 10.1093/toxsci/kfs236. Epub 2012 Aug 1. **A pharmacokinetic model of cis- and trans-permethrin disposition in rats and humans with aggregate exposure application.** Tornero-Velez R[1], Davis J, Scollon EJ, Starr JM, Setzer RW, Goldsmith MR, Chang DT, Xue J, Zartarian V, DeVito MJ, Hughes MF

Environ Health Perspect. 2010 Mar;118(3):345-50. doi: 10.1289/ehp.0901205. **Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 2003-2004 NHANES Data.** Xue J[1], Zartarian V, Wang SW, Liu SV, Georgopoulos P.

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	plasma compartment. The IEUBK is essentially a model of plasma exchange, with the long-term lead-binding constituents of the skeleton. As regard to specific comments, Approach 1 is focused on estimating a fraction of individuals that can be identified where elevated water lead levels will increase the probability of an elevated BLL by 1% or 5%. I am not aware of a risk-based interpretation of a level of lead in drinking water that results in a probability of a BLL being increased by 1 or 5%. A physiologically relevant health-based interpretation of a 1 or 5% shift is needed. The approach does not make clear what an appropriate baseline BLL should be. EPA should specifically discuss the rationale to establish a baseline BLL. Approach 2 is focused on identifying a concentration of lead in drinking water that shifts the geometric mean blood lead level by a defined amount. This approach, in theory seems more credible. However, this approach presupposes that a baseline BLL may be calculated assuming only the ingestion of Pb in water. This is both unrealistic, and not sufficiently conservative. Both Approach 1 and 2 seem to blur the distinction that the goal of the IEUBK model is not to align a "target BLL" to a specific child, but rather predict an average PbB (blood lead) concentration, or the probability that a child with a very specific exposure scenario would have an elevated PbB. Due to the kinetics of lead retention, distribution, and absorption, the proposed metrics do not appear to be appropriate *per se* "targets" when used in this manner. For example, an individual with an existing high blood lead level that is exposed to additional lead from drinking water may have a negligible increase in measurable blood lead (or % increase). For this individual, the lead may cycle/move from the blood to the bone (trabecular and cortical) as well as the kidney, liver, and other soft tissue and organs. It would be worthwhile to evaluate the IEUBK model parameters quantitatively (perhaps using a Bayesian approach that is similar to the one employed for the exposure inputs). Regardless of final approach, the IEUBK parameters should be more fully explored in terms of key parameters – such as blood to bone transfer and storage in infants. As the excretion of lead in the most sensitive population (infants) is very poorly understood, this appears to be a clear weakness of all modeled approaches that needs to be resolved. This may be significant as even the IEUBK model parameters set Pb excretory rates at the high end of values deemed plausible. A detailed review of intake or absorption values, as well as excretory parameters is warranted. Not otherwise discussed or considered is how the NHANES urinary lead levels in children may be used to consider variations in excretion, and may serve to inform model excretory parameters. While these data are not available for children 5 and younger, an analysis of existing data may have substantial impact on model predictions. The third approach, a hybrid of a probabilistic exposure assessment coupled to the IEUBK model seems most reasonable. Although, further explanations are needed as to the decisions (or empirical basis) to specify distributions for input variables, specify the model correlation structure, time steps, and the variance in BLLs. Additional analyses should consider an approach that takes full advantage of both IEUBK and SHEDS. For example, SHEDS could be used to predict various distributions from NHANES, and these

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	could be used as IEUBK model inputs. This approach would take full advantage of both models, and limit the limitation of each. Using the current approach, a probability-based approach to estimate exposure, may not adequately address exposure in individuals exposed to high levels of lead, and the use of only an IEUBK-derived "analytical solution" (a polynomial regression equation, and not the compartmental model) fails to take full advantage of the power of IEUBK to consider the kinetics of this type of lead exposure. Given the saturable and non-saturable absorption of lead, the individual parameters may have significant effects on the disposition of lead – especially in an infant.
Ryan	**a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.** The approaches attempt to address three different issues. Approach 1 looks at the likely distribution of an individual child's BLL and assesses whether a given drinking water standard will increase the probability of the child's BLL above a standard to produce an elevated BLL (EBLL) defined as 5 µg/dL, or ostensibly, any other chosen cutoff. Approach 2 looks at what level of drinking water lead would result in an increase of the expected value, i.e., the mean or geometric mean, BLL for a specific child might be moved by 0.5 or 1.0 µg/dL. These are different things. Approach 1 examines the effect of a given standard on the tail of the distribution of a child's likely exposure while Approach 2 attempts to understand the effect on the central tendency - the expected value - of the child's BLL. Approach 3 differs from the deterministic calculations outlined in Approaches 1 and 2, and looks at distributions across the national population using a simulation approach drawing upon large time-activity databases, and other parameters with variability. It then examines the impact of a specific standard - and its intrinsic uncertainty - and various population parameters, e.g., media, 75^{th} %, 90^{th} %, etc. The three Approaches are not directly comparable as they are designed to do different things and give different information. Approaches 1 and 2 can be discussed together as they both use the deterministic IEUBK model to investigate the BLL of a specific "representative child." But, again, they are different and address different questions. The probabilistic measures given in Approaches 1 and 2 stem from assessing a geometric mean and geometric standard deviation for a "representative child" then evaluating aspects of a lognormal distribution assuming these parameters. This is a reasonable approach, albeit one that is best thought of in a deterministic fashion rather than in a distributional fashion. One takes values from the literature regarding geometric means and geometric standard deviations, assumes an analytical form for the probability distribution, and calculates the values in question. Approach 1 then evaluates the probability of this lognormal distribution exceeding a specific value, nominally 5.0 µg/dL, but it really could be any test value. This value is completely determined by the geometric mean and geometric standard deviation determined from the input parameters gathered from the literature. In the same way, Approach 2 analyzes the distribution in a different way by assessing how large the drinking water standard would be so as to affect the central tendency estimate by a certain amount, namely 0.5 µg/dL or 1.0 µg/dL.

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	While doubtless accomplished in separate analyses, in principle, there is no reason both could not be done in the same modeling run by stepping through various drinking water standards then picking out the information needed from whichever one gave results of interest. Approach 3 is entirely different. It's using an intrinsically distributional approach by creating a large number of simulated individuals and observes the distribution of their BLLs. Input parameters are drawn from empirical time -activity profiles, physiological parameters, home characteristics, etc., to develop the distributions. It then takes these results and looks at percentiles of the distribution of likely BLLs for the entire population thereby examining the impact of a specific lead drinking water standard on the population distribution; SHEDS is a complicated program that requires a large amount of empirical data. As someone who has done a lot of simulation work in the past, I, of course, prefer the SHEDS approach to the deterministic approach of different implementations of the IEUBK stand alone. But all three approaches give information that is useful to the regulator. No single result is definitive; the three together are much stronger than the sum of the parts. Despite some comments by others that one, or the other of these approaches is better, I maintain my assessment that the three approaches offer complementary information and are all useful. My colleagues have persuaded me that Approach 3 is indeed the strongest of these Approaches, not that I needed much persuasion. However, Approach 3 is also the most difficult to implement, and the most time-consuming. Further, it requires either substantially more data, which may be site-specific, or a series of assumptions that may, or may not, be appropriate in a given instance. But I do maintain that unique information is obtained from each of the Approaches and that EPA should consider all three in its search for the best information. **b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.** The IEUBK is a well-developed and stable model of lead uptake in the human system. It produces estimate of the BLL estimates based on input parameters; it is deterministic. However, it contains a number of default assumptions including distribution among the various compartments of the body, that may not apply under specific circumstances, or, more importantly in the context of this modeling exercise, for different life stages. Further, it calculates a geometric mean and geometric standard deviation, then assumes a lognormal distribution based on those parameters. This results in reduced flexibility in the model. Why lognormal and not, say, gamma-distributed? Finally, the model was developed some 20 years ago; there may be updates of some of the parameters and perhaps a better understanding of the distributional characteristics of BLLs associated with the parameter inputs. This being said, to my knowledge, there is no better deterministic model out there for estimating BLLs than the IEUBK.

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	I maintain that the IEUBK is getting long in the tooth and may be in need of some reworking, especially in the biokinetic modeling. Advances over the last 20 years have been more than incremental and it may be incumbent upon EPA at this point to develop a new modeling systems, based on newer information about the adsorption, distribution, metabolism, and excretion of lead in the body. A fresh look, perhaps using different input/kinetic parameters and modification of assumptions could be in order. **c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).** The IEUBK-SHEDS approach tries to overcome some of the difficulties discussed above by using empirical distributions for any number of parameters and implementing an approach that affords a better estimate of population, rather than individual, variability. It also has the ability to produce percentile estimates for the population rather than deterministic estimates for an individual. Finally, IEUBK-SHEDS can be used to account for parameter uncertainty and its impact on the estimates. The deterministic approaches of IEUBK afford estimates of the percentiles for an individual, but does not have the capability of assessing uncertainty in the percentile estimates unless some type of brute-force variation in parameters coupled with sensitivity analyses are brought to bear. ***Much of our discussion focused on the use of the IEUBK-SHEDS Approach, Approach 3, in this review. My colleagues were persuasive in their arguments that this was the Approach most likely to yield the best modeling system for assessing lead in drinking water. While Approaches 1 and 2 can yield both deterministic and distributional characteristics for exposures, they do the latter in an artificial manner by assigning a fixed distribution type, i.e., lognormal, to the exposures likely experienced. Further, the change from the mean as a measure of central tendency to the median is problematic as the IEUBK Model assumes the former and the biokinetic parameters are developed accordingly. Approach 3 offers a better mechanism for assessment but at a cost, as discussed above: increased complexity and the need for more input information of additional assumptions. I came to the meeting believing that Approach 3 was the best Approach, but the others offer additional information. I came away with essentially the same thought, although I am more convinced now of the superior nature of SHEDS-IEUBK Approach. Nevertheless, I encourage EPA to continue evaluation of all three Approaches. I may be in the minority in this view as I believe my colleagues may be more attuned to an exclusive use of Approach 3, although I may be misinterpreting some of their arguments.***

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Vork	**a. Compare and contrast each approach and comment on the strengths, weaknesses, and uncertainties of each as well as the utility of the different ways the outputs are presented.** Comment: Each approach has merit and informs risk managers at national, state and local levels. It is clear that efforts at Federal, State and local levels continue to be vital in preserving the public's health. Approach 1 is a useful screening tool at water district and local levels. Approach 2 relates to approaches used, for example, in California to determine the public health goal for lead in drinking water and for other programs at the state and local level. Approach 3 provides a means 1) to assess the general level of lead exposure from environmental sources across the nation and 2) assess what water concentrations would need to be to help prevent blood lead exceedances at the population level. Each approach also has limitations and uncertainties. Adjustments for safety and uncertainty would be an important component to incorporate in each approach. **b. Please comment on the strengths and weaknesses of using the IEUBK model to predict drinking water concentrations that may result in specific increases in BLLs and/or increased probability of elevated BLLs.** Comment: The greatest strength of the IEUBK model is its ease of use. The examples in this report of predictive success seem reasonable. However, compared to the IEUBK model, the Leggett model (for example) is completely transparent and changeable. Whereas over half of the IEUBK model parameters are fixed. With an open code model there are more options to explore. For example, children with multiple years of exposure, changes in time averaging can be explored along with other important biological variables such as body weight and hematocrit. It may be important to explore whether infants and children on the extreme end of factors such as low birth weight, high background lead burden prior to start of exposure period of interest, low hematocrit etc. are covered by a composite GSD. **c. Please comment on the potential utility of using the SHEDS-IEUBK approach (currently used in Approach 3) to develop an estimate of the concentration of lead in drinking water associated with a percentage increase in the probability of an individual child experiencing an elevated BLL as is done in Approach 1 (using only IEUBK). Please also comment on the utility of using the SHEDS-IEUBK approach to identify the concentration of lead in drinking water associated with a specified increase in the geometric mean (GM) BLL for a population exposed to lead in drinking water as is done in Approach 2 (using only the IEUBK).** As tap water becomes an increasingly minor contribution to blood lead, model predictions are more difficult to check with measurements because of the "noise" in the data. However, the SHEDS-IEUBK model may best serve a population that experiences a

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	substantial increase in lead levels in tap water. The IEUBK model is easy to use as a screening tool.

1.4 MODEL EVALUATION AND MULTIMEDIA EXPOSURE PATHWAY/SENSITIVITY ANALYSES

Please comment on the strengths and weaknesses of the three approaches considering existing blood lead data. Please also comment on the strengths and weaknesses associated with the approach to modeling the relative contributions by exposure pathway. Please comment on what type of sensitivity analysis would be useful to analyze aggregate lead exposures and identify key model inputs, and on the sensitivity analyses conducted for Approach 3.

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Georgopoulos	The responses to the previous questions have already described the reasons Approach 3 provides a more comprehensive and scientifically defensible framework that can calculate BLLs for direct comparison with existing (NHANEs and NHEXAS) blood lead data. NHEXAS offers the additional potential advantage that individual-specific exposure information can be linked to biomarker (BLL) data, while this potential is generally not associated with NHANES data. On the other hand, the "magnitude and continuity" of the NHANES database make it the "gold standard" for evaluating modeling predictions. However, as repeatedly mentioned in the responses to the previous questions, the existing blood lead data are only representative of the population (e.g. NHANES) sampled and do not reflect a distribution of the US population. In any case, agreement of probabilistic/distributional model predictions with corresponding existing (NHANES, NHEXAS) blood lead data builds confidence to the model and justifies (with recognition of the appropriate caveats) its application to ranges beyond those corresponding the aforementioned databases. Both "local" and "global sensitivity analysis" can (and should) be utilized in gaining a better understanding of the key inputs and parameters affecting the outputs of IEUBK, SHEDS and of their combined application. Local sensitivity analysis involves multiple perturbations around a nominal point of the model's response surface, while global refers to sensitivity analysis across the entire response surface (see, for example, page 71 of USEPA, 2009, Guidance on the Development, Evaluation, and Application of Environmental Models, EPA/11/K-09/003; also, any standard reference, such as, e.g. Saltelli et al. 2004 or Saltelli et al. 2008). It is recommended that, for the application currently considered, at a minimum a systematic set of One-at-A-Time (OAT) sensitivity calculations are performed. OAT calculations are the "most tractable" sensitivity calculations, as they select a "base case set" of input values and perturb each input variable by a given percentage away from the base value while holding all other input variables constant. Such sensitivity calculations yield "biased" local measures of sensitivity (no matter how "large" or "small" a perturbation they consider), that depend on the choice of base case values. One way to avoid this bias is to use the "Morris's OAT" scheme for screening purposes because it is a relatively simple global sensitivity analysis method: it "entails computing a number of local measures (randomly extracted across the input space) and then taking their average" (see, e.g. USEPA, 2009). So, Morris's OAT

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	provides a measure of the importance of an input factor in generating output variation, and while it does not quantify interaction effects, it does provide an indication of the presence of interaction (see, e.g. Wainwright et al., 2014). It is strongly recommended that the work under review considers employing a global sensitivity analysis such as, specifically, Morris's OAT. OAT can provide useful insights for IEUBK modeling. In the case of SHEDS, with proper sampling (and maybe with certain code modifications) the Monte Carlo simulations can provide sufficient response information for the entire sampling space of the variable of concern, that can also allow the construction of global sensitivity metrics.
Goodrum	The SHEDS-IEUBK approach provides the most robust evaluation of relative contributions of variables and pathways to intake, uptake, and BLL. The output (BLL distribution) can be parsed into different percentile ranges to even more closely examine how the relative contributions may change as a function of, for example, quartile of predicted BLL. This is more robust than the one-at-a-time methods that are accommodated with IEUBK model runs. However, I view this feature as "nice to have" but not necessary to answer the central charge question of what the concentration in water might need to be in order to achieve a health-based benchmark. Approach 2.5 introduced above capitalizes on the NHANES data as being representative of baseline conditions. To some extent, these conditions likely reflect a non-zero contribution of water already, so adding in another water pathway may amount to double-counting. This is unlikely to affect risk metrics based on "delta PbB", but it could be viewed as conservative (likely to overestimate risk) for risk metrics based on absolute BLLs like 3.5 and 5.0 µg/dL. It is helpful to examine the sensitivity of the results to a range of plausible GSDs. This is true for any IEUBK modeling run, but particularly true here. Note that the GSD of 1.6 is representative of the distribution of BLLs for children who are similarly exposed. Therefore, we can establish baseline, using different percentiles from NHANES (e.g., quartiles) as scenarios representing communities that may have a range of GM BLLs. As the contribution from baseline increases, the health-based benchmark will decrease for risk metrics that are based on the absolute BLL. But for risk metrics based on delta BLL, the health-based benchmark will be less sensitive to the choice of summary statistic used to represent baseline.
von Lindern	In the report, although denying that the EBLL and "target" %-tiles to exceed criteria are not health related, EPA makes the following assertion with regard to Approach 3. *"In addition, population-based approaches are consistent with previous EPA methods for assessing lead exposures."* As noted above, EPA states this is only a statistical exercise, but nevertheless is developing a methodology with profound health implications. This makes it difficult to provide specific comments regarding the inputs to, and interpretations of, the output from these models without substantial caveats. It is also a methodology with a long and sometimes

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	contentious history. A brief review of the evolution of this strategy may help to understand this dilemma with respect to use of current blood lead levels. EPA has used percent to exceed blood lead health criteria in regulatory applications for the past 40 years beginning with the NAAQS in 1977. At that time, the air quality standard was developed with the objective of keeping 95% of children nationally below a 30ug/dL blood lead level. Recognizing the relatively consistent lognormal distribution of blood lead levels in similarly exposed populations, required that the mean national children's blood lead level not exceed 15ug/dL. In EPA's view this allowed an air-sourced increment of 3ug/dL when added to the 12ug/dL national average. EPA's policy at that time was that the 12ug/dL average was due to sources other than air, and that the children in the 95th plus percentiles of the distribution were influenced by exposure co-factors that also could not be mitigated through regulation of air lead levels. The development of initial IEUBK model by the EPA's Office of Air Quality Planning and Standards (OAQPS) in the mid-1980s was the initial attempt to quantitatively consider multimedia sources and incremental impacts of individual sources on blood lead levels. By this time, the health and scientific community, and the Agency, recognized that irreversible deleterious health effects occurred at lower levels than previously detected; that the log normal characteristics of the population blood lead distributions were (in part) due to multiplicative effects of intake rates and exposure co-factors; and the dose-response was non-linear. By 1984, the blood lead health criteria were lowered to 25ug/dL, a level no individual child should exceed. However, the EPA regulatory approach continued to apply this target to 95% of the population, as it was believed that the blood lead levels of children in the upper percentiles could not be effectively addressed by further reducing media concentrations, again as the high intake and absorption rates were due to exposure co-factors; and those co-factors were often related to peculiar behavioral or socio-economic conditions. By 1991, the IEUBK was being applied in risk assessment and mitigation efforts in other Agency programs and the operative blood lead criteria was 10ug/dL for 95% of the population with no child exceeding 15ug/dL. The CDC directive on which EPA relied indicated adverse effects of lead occur at blood lead levels at least as low as 10 µg/dL; but a blood lead level < 10 µg/dL was not considered to be indicative of lead poisoning. CDC also indicated that it was unlikely that single media sources of blood lead levels in the 10-14ug/dL could be identified and remediated (i.e., lead concentration reduced) to mitigate the risk; and that intervention and counseling efforts to modify behavioral and socio-economic considerations should be applied. It followed that over the next decade the risk mitigation strategies developed at many EPA CERCLA and RCRA program sites employed a dual strategy of (i) reducing media concentrations to effect lower mean blood lead levels that would result in 95% of children having a predicted blood lead level below 10ug/dL and (ii) a concurrent lead health intervention program to effect beneficial behavioral modifications for families with children above 10ug/dL and medical intervention for children above 15ug/dL. The IEUBK was extensively used in both risk assessment and mitigation, particularly for identifying media specific cleanup criteria (or media concentration levels). In later years, the EPA modified the IEUBK risk analyses to require a 95% probability of a blood lead level <10ug/dL for each individual child in a population, as opposed to 95% of the entire

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	childhood population. This resulted in significantly more stringent cleanup levels (i.e., it required lower media concentrations), as the percentile now applied within the most vulnerable age groups of 2-3-year age children, not across the 1-7-year age population originally evaluated. This EPA policy history is important to consider in light of the perceived eventual use of the "percent to exceed health criteria" from the proposed IEUBK drinking water models in comparison to current blood lead levels. In past applications, EPA has used the 95th percentile of the blood lead distribution to define the maximum allowable media concentrations necessary to lower the central tendency (or population mean blood lead level). This document does the same, but asserts it is to accommodate observed 97.5% upper limits of the NHANES populations, as opposed to health criteria. This is accomplished by recognizing the log normal characteristics of the response variable and applying the appropriate geometric standard deviation (gsd). Implicit in the EPAs historic approach (and perhaps not acknowledged in this report) is that the risks to the 5% exceeding the blood lead criteria are not efficiently, nor sufficiently, addressed by further lowering the media concentrations (i.e., the "tail" is excluded from determining the standard). The modeling strategies proposed in this review, however, seem to suggest that the analyses are being driven by trying to fit the 97.5%-tile of the NHANES population, and that responses within the "tail" have been used to modify the input parameters, and ultimately determine the appropriate media concentrations. Several Public Comments noted the uncertainty, lack of reliability, and sensitivity of these high percentile blood lead estimates and subsequently the target "health based benchmark, or household action level" drinking water action levels derived from the tail of the distribution. This report suggests an underlying objective of modifying these evolved risk assessment methodologies is to fit the tail of large national data bases collected and assembled for other purposes by diverse methodologies. Additionally, the inclusion of the soil/dust ingestion rate distribution with a large gsd derived from a behavioral modeling study required using a low geometric mean central tendency value that corrupted the Approach 1 and 2 results. One can't resist pointing out this may represent a classic case of "the tail wagging the dog". If the history of the distributional aspects of blood lead reduction in the US over the past decades is any indication, regulating concentrations in any environmental source media can have a significant effect on reducing blood lead levels for about 90-95% of the children in the contemporaneous distribution. The children in the higher percentiles suffer multiple atypical source and exposure co-factors, that cannot be remedied by further reductions in that media concentration. On the bright side, history also shows that effecting source reductions in one medium shifts the national blood lead distribution, making it possible to achieve further reductions by addressing other media, bringing more children in the tail below the threshold criteria. Unfortunately, there is no safe threshold and this trend will continue until zero blood lead and near zero (perhaps requiring pre-industrial geologic background levels for environmental media. Perhaps, now it is the safe drinking water program's turn to shift the distribution. EPA's task should be to identify and implement that combination of source control (health benchmark) and affected population that maximizes protectiveness. And, at the same

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	time EPA should identify those remaining victims of lead poisoned children that responsible public health practice obliges civilized societies to address through other intervention strategies.
Loccisano	Sensitivity analyses should be conducted for all parts of modeling (physiological, pharmacokinetic, and exposure parameters). Local analysis will address sensitivity relative to point estimates of parameter values and global analysis will address sensitivity relative to the entire parameter distribution. Sensitivity analysis will obviously identify which parameters have the greatest impact on model output, and if those parameters have significant uncertainty associated with them, those can be focused on for refinement. In approach 3, the sensitivity analyses appear to be conducted for only the media concentrations of lead (water Pb, soil Pb, etc), ingestion rates, and absorption rates; it is not clear to me if other parameters were varied and the model output was examined for these. As stated above, sensitivity analyses should be carried out for all model parameters. Also, sensitivity analysis should be conducted with the maternal BLL as this will ultimately affect the child's baseline BLL. NHANES BLL data are comprehensive so this is a reasonable data set for use in model validation and also for establishing baseline BLLs. However, there are other BLL data available (such as NHEXAS and probably other federal and state data); all three approaches should be run against these other data sets for validation. Obviously, if the model yields satisfactory predictions for multiple data sets, confidence in the approach is increased. If local data from a highly exposed community are available, this would be useful in establishing baseline BLLs for that particular area.
Nascarella	The description of blood lead levels in this document seems to ignore the fact that lead-based paint is the primary source of lead exposure for young children. The dominance of this exposure pathway is complicated to communicate alongside a message that all lead exposure for children should not be controlled or eliminated. No safe level of lead has been identified and all sources of lead exposure should be eliminated. This concept is not adequately explained in the document, and has the potential to divert significant resources and attention away from a very important public health issue – homes containing lead paint. This will add confusion to existing public health-focused efforts in communities of high risk of childhood lead poisoning, and distract from risk communication and risk mitigation actions at the household and school level. There are many local, state and federal sources of information that would support a robust analysis of the sensitivity of the contribution of environmental media to elevated BLLs. For example, CDC has been collecting blood lead data on children since 1997 and maintains an extensive database. In fact, about 2.5 million blood lead tests are received by CDC each year. While these data are fundamentally different than the NHANES population-based health study designed to assess all children in the United States, these Childhood Lead Poisoning Prevention Program (CLPPP) data should be more fully explored. For example, EPA should consider how combining CLPPP data from different sources, at various levels of geographic and temporal specificity, may inform an assessment of how to accurately "target" a candidate BLL (or percentile/central

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	tendency estimate), such that a change in water lead level may have meaningful impact on lowering BLLs. Data to support this type of study are available from a variety of CLPPP data sources (CDC, 2013). Previous analyses have shown significant departures from NHANES estimates. For example, approximately 11,000 higher-risk children and adolescents tested at an urban medical center had significantly higher BLLs than the corresponding NHANES references values with a geometric mean BLL of 3.2 µg/dL in males and 3.0 µg/dL in females (Soldin et al., 2003). The absorption of lead from the gastrointestinal tract will vary depending on the contents of the stomach. A better description of how food in the stomach was considered in the model scenarios is important. As a 90% bioavailability for fasting children is not unreasonable, the sensitivity of the model to this consideration is important. A sensitivity analysis should also be performed on the water ingestion rate for infants, specifically the sensitivity of the model to estimates such as 0.526 vs. 0.64 L/day. The sensitivity of the models to the maternal blood lead level should be evaluated. For example, I would evaluate the sensitivity of this assumption to both a broader definition of "childbearing age" – to align with biological capability – perhaps begin at 15 years old (Johnson et al., 2006). I would also evaluate the sensitivity to an estimate that captures the fact that mothers are now typically older (see National Vital Statistics System and National Survey of Family Growth data; for examples see CDC, 2017). The approaches rely heavily on the IEUBK Model. This model's principal application is to model the physiological effects of lead exposure where there are long periods of relatively steady-state exposure. This is based on the assumption that equilibrated blood lead levels after chronic intake are associated with certain toxic effects. Certainly, any approach that will be used to revise the current lead regulations needs to consider this type of steady-state (chronic) exposure, as well as the transient exposures to high levels of lead (presumably from particulate-related spikes in Pb water concentrations). The model needs to be evaluated in terms of the uncertainty of this exposure parameter. As described above, any proposed approach, needs to be evaluated in terms of the sensitivity to changes in the IEUBK parameters. Many of these parameters will also require an uncertainty analyses (bone transfer kinetics). The approaches could also be improved by a detailed analysis of the voluntary water quality data that has been generated since the revised Drinking Water Action Plan in November 2016. A tremendous amount of public data are now available to better understand the variability of lead levels in drinking water within entire distribution systems. Certainly, much of these data (worst case "first draw" values) could be considered in the IEUBK model as part of an option for the user to specify a first-draw on a home faucet or school water fountain (e.g., Equation E-6 in IEUBK – FirstDrawConc).
Ryan	I should think that the best approach in all three cases is to validate the models against existing data. This can best be accomplished by using BLL data and any other characterizing data to validate the IEUBK model. For example, one could take a relatively large sample of individuals with measured BLL and collect data on external

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	parameters thought to influence such. This would include drinking water concentration, activity profiles, housing characteristics, etc. I assume that this is how the IEUBK model was validated initially. Given a large enough database, after completing that task, one could match external characteristics of individuals with one another, save the single characteristic under investigation. As an example, consider drinking water concentration. As a subset of those measured, match individuals according to housing characteristics and other measures such as dust and soil concentrations. Then categorize them by drinking water concentration. One then would essentially have "controlled" for all of the other characteristics and could examine the effect of drinking water concentration on BLL. Alternatively, one could take such data and implement a statistical rather than heuristic, approach through, for example, a regression model of the type: $$\mathrm{BLL_j} = \sum_i \beta_i \mathrm{X_i} + \beta_{\mathrm{DW}} \mathrm{DW_j} + \varepsilon_j$$ where $\mathrm{BLL_j}$ is the observed BLL for the j^{th} individual, X_i are the characteristics other than the drinking water concentration that one wants to "control" for that individual and DW_i is the drinking water concentration for that individual. The β_i are the effective contributions of the exposure factors to $\mathrm{BLL_j}$ and β_{DW} s the drinking water contribution to $\mathrm{BLL_j}$. The ε_i represent individual-specific errors in the regression model. One could then evaluate the marginal effect of a change in drinking water concentration would have on BLL. Sensitivity analyses using IEUBK or SHEDS-IEUBK is most easily effected by using a variation of parameters approach to evaluate uncertainty. Distributional characteristics for the population are already built into the system. Alternative methods may afford a more rapid evaluation of the importance of given factors. For example, a change of 10% in a parameter could be evaluated. If the change in BLL were small, then one could ignore the changes in this parameter for future analyses (See discussion below on factorial design.) ***I think there was general agreement among my colleagues that a sensitivity analysis is necessary for all three Approaches. Indeed, Drs. Zartarian and Xue in their presentations and discussion indicated that such was either underway or had been done. I have outlined a few approaches in my pre-meeting comments, and others were addressed in the meeting. EPA staff, I believe, are amenable to continued development along these lines and such development was strongly encouraged by the group. I concur with this suggestion and add my full support to this direction for modification and expansion of this work.***
Vork	I defer to others on the panel who are more familiar with conducting sensitivity analyses on complex models. In my limited experience, a targeted sensitivity analysis guided by prior knowledge of sensitive parameters can be an efficient approach.

1.5 How could each of these approaches be improved for the purposes of evaluating drinking water concentrations associated with increased/elevated BLLs? For each of these approaches, how could one account for the variability of drinking water concentrations measured at homes during sampling, in research studies, or predicted using modeling techniques?

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Georgopoulos	In this reviewer's opinion, improvements should focus on Approach 3, which is the most scientifically defensible and has the potential of explicitly accounting for variability (including variability of drinking water concentrations measured at homes during sampling) and uncertainty via the two-stage Monte Carlo framework built in the SHEDS model. Both variability and uncertainty can (and should) be addressed in a two-stage Monte Carlo approach. Chapter 2 of USEPA's Exposure Factor Handbook (USEPA 2011) states (on page 2-1) that "[P]roperly addressing variability and uncertainty will increase the likelihood that results of an assessment or analysis will be used in an appropriate manner. Characterizing and communicating variability and uncertainty should be done throughout all the components of the risk assessment process (NRC, 1994). [...] Proper characterization of variability and uncertainty will also support effective communication of risk estimates to risk managers and the public. [...] U.S. EPA (1995), following the NRC (1994) recommendation, has advised the risk assessor to distinguish between variability and uncertainty." The same USEPA document (EFH, on page 2-5) describes the four-tier approach of the International Program on Chemical Safety (WHO, 2006) for addressing uncertainty and variability, that is also consistent with USEPA practices and recommendations: The four tiers include "the use of default assumptions; a qualitative, systematic identification and characterization of uncertainty; a qualitative evaluation of uncertainty using bounding estimates, interval analysis, and sensitivity analysis; and a more sophisticated one- or two-stage probabilistic analysis." Although SHEDS provides these options, the application currently under review does not explicitly address uncertainty; this should be addressed in any future work on this matter. Responses to previous questions already considered the need of improving both input databases and input practices, by explicitly recognizing (listing and explaining) and consistently handling issues associated with • (a) treatment of non-detects, • (b) presence of correlations in distributions of inputs that reflect exposure factors (as well as other, e.g. biological, parameters), and • (c) limits/ranges of applicability of empirically derived ("fitted") regression equations used to parameterize inter-individual and intra-individual (e.g. temporal/behavioral) variability (again, both with respect to exposure and biological factors). Development of population-relevant distributions of BLLs via Approach 3 (or via future refinements of Approach 3) can provide a useful tool for the support and assessment of health-relevant (or health-based, though, ideally that would require the explicit

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	incorporation of mechanistic adverse outcome pathways linking exposure to biological effect through the BLLs) benchmarks for lead in drinking water. An extensively tested multimedia/multipathway framework for aggregate lead exposure modeling can provide valuable support for comparative evaluation of alternative mitigation options that include the drinking water pathway.
Goodrum	I interpret this question about variability of drinking water concentrations at homes to mean that there is an inherent uncertainty in relating modeled estimates of exposure and risk to actual exposures that may occur in residential settings. With IEUBK, as with many exposure models used in risk assessment, the concentration term represents the long-term average concentration over a period of many months or years. It does not explicitly model short-term fluctuations or temporal patterns in concentration, but rather, assumes that the relevant metric is the long-term time-weighted and volume-weighted concentration. It is acknowledged that real-world exposures are intermittent (not continuous throughout the day) and may vary in both intensity and frequency. I did not interpret "variability in drinking water concentrations" to imply that there are different exposure point concentrations at different households, which contributes to interindividual variability in exposure point concentrations. This interindividual variability does not need to be represented in the context of the use of the models to back-calculate a health-based benchmark for water. Thus, the essential question is framed as follows: *What concentration of lead in water is protective of a specified blood lead reference value?* The three approaches outlined in this report each examine variations of risk metrics based on the probability of exceeding a BLRV. There are several approaches that can be considered to evaluate temporal variability, briefly discussed below. I do not believe that this issue represents a major source of uncertainty in the application of the models for the purposes of defining a health-based benchmark for lead in water. The models as proposed can be used to effectively represent a range of different potential long-term average concentrations. The guidance that accompanies the models can explain that, in practice, it is expected that there is short-term temporal variability in the exposure concentrations associated with drinking water that contains lead, which may result in short-term variations in BLLs. a. Stochastic simulation – while we could use stochastic models to simulate long-term average exposures from a series of short-term exposure periods (e.g., micro-exposure event modeling – see Goodrum et al. 1996; Griffin et al. 1999; USEPA 2001), there is insufficient information on the kinetics of lead absorption, distribution, and elimination over such short time periods to believe that this added complexity reduces uncertainty. Furthermore, examining the fluctuations of BLLs over short time periods is not recommended. USEPA (2003, p.11) notes that the health effects (acute or chronic) of peak BLLs that occur after acute exposures are not well understood. b. Model different locations – it's possible that individuals are exposed to lead via drinking water from different locations (e.g., primary residence, residence of a family member, day care, school, public buildings). USEPA (2003) provides

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	guidance on use of the IEUBK model to simulate time-weighted exposures to lead in soil for scenarios where an individual engages in activities at a location at least one day per week for a period of at least three months. The same approach could be used to address lead in water. National surveys of activity patterns of the U.S. population could probably be used to simulate the plausible range of exposure scenarios among the U.S. population. In addition, we could probably also simulate the plausible variations in the concentration term at these different locations. However, from a public policy perspective, a risk assessment that supports a health-based benchmark that is protective of a scenario where an individual consumes all of their water from one source will also be protective of every combination of scenarios where they consume water from multiple sources (some of which may have lower concentrations of lead in drinking water). In short, it is conservative to assume a 100 percent fraction from the source with the highest concentration of lead. So, in my opinion, it is not necessary to add an activity pattern scenario that considers multiple locations of water consumption to the set of simulations in this report. c. Model the acute exposure scenario – The model can be used to simulate seasonal variability such that we can consider the time period when the highest concentrations may be present in drinking water (or the combination of concentration and consumption rate yields the highest average daily intake rate). As noted above, the IEUBK model can be run to simulate exposures that may occur over a minimum of a three month period and guidance is available on this application. Khoury and Diamond (2003) and Lorenzana et al. (2005) both present an analysis of short-term exposures to lead to illustrate that short periods of acute exposure can yield peak BLLs that are greater than peak BLLs predicted using IEUBK. To evaluate such acute scenarios, the ICRP model (developed by Leggett and coworkers) was used, which can simulate exposures to lead using a daily time step. USEPA has been testing the ICRP model for use as an "All Ages Lead Model" for lead, or AALM. A beta version of the model underwent external peer review in 2005-2006 (USEPA 2006) and, although not yet released to replace IEUBK and ALM, has been applied by various research groups as recently as the past couple of years (McLanahan et al. 2016; California EPA 2016). Lorenzana et al. (2005) carefully examined the difference between adjusting the IEUBK model to account for short term, elevated exposures (by adjusting input variables) and simulating exposures with the ICRP model which uses a daily time step. Several observations were noted, which are relevant to the question raised in this charge question: 1. Defining inputs to represent a one-year averaging time (such as with the standard IEUBK application) may underestimate BLLs if there are sustained periods of elevated exposure, such as a seasonal pattern in lead uptake via water.

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	2. The magnitude of the underestimate depends, in part, on the relative contribution of the baseline exposures – in this case, baseline would be attributable to all non-drinking water exposure pathways. As the relative contribution of the baseline exposures to the total exposures increases, the potential for seasonal peaks becomes more important because the incremental contribution that can come from drinking water is reduced. This would be true for each of the risk metrics represented by the three approaches examined in the report. 3. One or more of the input values for exposure variables in the IEUBK model can be adjusted to represent the average over a shorter time period than one-year. Compared to a model like ICRP, which can simulate daily exposures, IEUBK run in this mode would be expected to yield higher BLLs. This could be viewed as conservative (health protective), but without running side-by-side comparisons, it would be challenging to quantify the magnitude of the difference. The bottom line is that temporal variability in concentrations and drinking water ingestion rates could be important. Seasonal variability in concentrations in water would not actually affect the health-based benchmark itself; this would be more of a risk management consideration – that is, how should tap water sampling be conducted in order to achieve compliance (e.g., during the season when peak levels are expected to be present). Seasonal variability in water ingestion rates can be handled by specifying an ingestion rate that corresponds with the peak seasonal ingestion. The IEUBK model can continue to be used to explore this question, given that when it is run with appropriate inputs that reflect short-term (higher) averages, it will likely yield higher concentrations than ICRP. However, a rigorous sensitivity analysis would require an alternate modeling platform such as ICRP given the limitations in the model framework of IEUBK.
von Lindern	*Improvements:* Approaches 1 and 2 could be improved and made health-relevant by using more appropriate consumption input parameters and applying these to stratified exposure scenarios that reflect more sophisticated soil/dust concentration profiles with both home and community partition components. Ingestion rates could be increased to levels reflective of the more recent literature. Committees currently evaluating ingestion rate recommendations for the IEUBK and Exposure Factors Handbook should be consulted. Geometric means should not be considered without careful examination and probable readjustment of the biokinetic and distributional components of the IEUBK. Although soil dust data may be difficult to obtain and organized, modeled estimates based on variables in addition to house age would improve the analyses over the simple point estimates applied in this report. The soil and dust concentrations should be developed by combining both home, yard, neighborhood and community-wide characteristics. It would be best to enter these soil/dust exposure

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	profiles to the IEUBK in batch mode, in proportion to the abundance of each exposure stratification in the US population (or NHANES database) for comparative purposes. The drinking water consumption rate conflicts with those used in other programs and should be resolved. An Agency-wide supported value(s) should be used, as the determination of the appropriate benchmark will be directly proportional to the consumption rate value. The results of Approaches 1 and 2 could also be presented in terms of the stratified analyses to examine the impact of different drinking water concentration levels among diversely exposed communities in the US. The SHEDS analyses could be amplified to include alternative distributions of ingestion rates, and the results examined through sensitivity analyses assessing the impact of other input variables in explaining apparent over-prediction of blood lead predictions with the NHANES database. Additional sensitivity analyses should be run on combinations of consumption variables and concentration profiles. More sophisticated media concentrations should be developed and sensitivity to various elements of these distributions should be conducted. *Variability in drinking water data (homes vs systems):* More detail should be provided regarding the frequency and magnitude of elevated water concentrations and the relation to exceedances of the action level (AL) and water purveyor's monitoring and follow-up requirements. The Benchmark should be developed within the context of the AL. High values observed in distribution systems should be investigated and permanent solutions encouraged or required; and periodic lowering of the AL should be considered as water systems evolve, older lines are replaced. The Benchmark should be developed to allow users to weigh the health risks of elevated water concentrations in their homes and schools in their own communities against the health benefits and costs of corrective actions. The Benchmark values derived from any of the approaches will inherently reflect the exposure periods anticipated in the IEUBK model. Formally, these exposure estimates assume a series of lifetime annual averages to accommodate the yearly blood lead estimates provided. Practically, blood lead levels for young children reflect recent absorption likely on the order of months to, perhaps, a year. EPA appropriately used the 30-day exposure averaging time noting recommendations of an external peer consultation panel. Thus, the benchmarks should reflect some type of rolling average on the order of 30 days to a year. The difficulty, as several public commenters noted, is that these values cannot readily be compared to typical water testing results reported by utilities or schools. Single high values encountered in routine monitoring are not uncommon; but a series of follow-up negative samples is not sufficient to make determinations regarding compliance with longer demand weighted averages. Sampling at individual service taps is so infrequent that most excursions to high levels will go undetected. The frequency of sampling required to obtain reliable 30-day rolling averages for each exceedance would be a waste of resources and an impossible burden. As a result, EPA could consider a monitoring scheme that requires periodic representative sampling of stratified exposure scenarios based on risk co-factors known to effect high lead levels (e.g., age of housing, corrosive water, lead service connections, quality of infrastructure,

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	etc.). If high levels are encountered, protocols for follow-up in similar communities could be developed. Because a single high value reported can be cause for family and community concern, a compositing protocol for follow-up on high values should be required, designed to both obtain reliable demand-related average concentrations, and confidence among users. EPA should consider pilot studies in high-risk communities exhibiting fluctuating water lead levels at a substantial percentage of community taps. These pilot studies should address both a survey technique to identify the frequency of excursions in a community, and appropriate follow-up strategies to develop reliable average concentration estimates, and provision of alternate water supplies, if required.
Loccisano	Each approach has utility in that they all address different questions. Approaches 1 and 2 are similar in that they both use the IEUBK model alone and examine a "representative child". Approach 3 is a probabilistic approach in that the SHEDS model is used, but as only variability in exposure (and not physiological/biological variability) is considered, I do not consider this a truly probabilistic approach. As someone who regularly does simulation/modeling work, I prefer Approach 3. However, although each approach can help inform risk assessments by providing different information, I do not think that any of these approaches can really be used alone. In order to incorporate variability (in water concentrations, other environmental media concentrations, and biological variability), a PBPK model coupled with Monte Carlo analyses could be used. A model like this will be more complex, but code for various lead PBPK models is available, can easily be implemented at EPA, and can better address variability and uncertainty. While the IEUBK model is easy to use, it is a "black box"; many parameters are fixed and the source code cannot be modified by the user. Models such as the Leggett, Rabinowitz, or O'Flaherty models can be modified by the user, which makes them much more transparent and allows for more flexibility in parameter values. Also, with model validation, the code can be modified in order to update biological processes (absorption, distribution, etc) that describe the disposition of lead in the blood and other tissues in order to better describe the validation data (I am not saying the model should be modified in order to simply fit the data here, but if new information becomes available on kinetics, that can be incorporated into the model code).
Nascarella	It is clear that the overarching EPA policy is that the safe level of lead is zero, and the EPA Office of Water will continue to communicate to states, drinking water systems, and the public that the goal (MCLG) is to have a "safe" level of zero lead in drinking water. As this is an aspirational goal, the modeling approaches were reportedly developed to provide states, public water systems (PWS), and the public with a greater understanding of the potential health implications when levels of lead are identified in drinking water. As such, all of the presented approaches, at a minimum, need to be improved if they are to be used to inform public education requirements, prioritization of households for lead service line replacement, or other risk mitigation actions at the

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	household or school level. For example, Approach 1, uses as a health-based benchmark a "1% or 5% increase in probability" of having an elevated BLL and Approach 2 uses an increase of 0.5 or 1 µg/dL as the health-based benchmark. It is not clear to me how EPA would describe the health bases for these particular metrics? Are these increases in a meaningful health-based outcome (e.g., an equilibrated BLL that would lead to an adverse impact such as an IQ deficit)? As a very practical and important matter, how would one begin to describe to a group of very concerned parents that their child's exposure to lead will result in a 1% increase in the probability of having an elevated blood lead level? Failure to adopt an approach that can adequately explain this fundamental question has the potential to divert significant attention away from a very important public health issue – childhood exposure to deteriorated lead paint, and the resulting dust and soil. This is because a blood lead based approach, if not properly communicated, will confuse and conflate childhood lead poisoning with lead in drinking water. For example, a highly probable scenario is one where a very concerned parent, one whom just learned that their child's exposure to lead will result in the "probability of having an elevated blood lead level" will immediately proceed to have their child's blood lead tested (or request it from a municipality/physician/state/federal agency)? If that value comes back high (i.e., 5 or 10 µg/dL), I suspect that the parent may immediately ascribe that elevation to the drinking water exceedance that they were just notified about. EPA should be mindful of how any final approach can be explained in this scenario. Is an elevated level of lead in water what EPA would describe as the most likely contributor to a blood lead level? Is a public health intervention focused on reducing exposure to water that has the "probability of resulting in an elevated blood lead level" going to provide a meaningful change in an individual's blood lead level? Will it provide a change in a population estimate? Some considerations when refining the presented approaches are listed in the bullets below. • An effective communication plan that addresses the complexity of this issue is paramount when seeking to address public concerns. When communicating exceedances of the current (non-health-based) lead action level (15 µg/L), the current health-based paradigm of "no safe level of lead" is often misunderstood to mean "any level of lead exposure is going to cause me harm". As the current lead action level is not health based – putting a level (magnitude) of exposure into a health-based interpretation will both assist with communication and prioritization of actions. Given this, a final approach that is articulated to these stakeholders should: o Describe how an exceedance is communicated in a manner that considers how lead exposure is ubiquitous, and that individuals are exposed from a variety of sources. ▪ For example, approximately 20% of children under 7 years of age are consuming at least 5 µg/day of lead through the diet. Put into a drinking water context - for a 5-year old child, that consumes 0.2 L of water per day, that is equivalent to drinking water with a lead concentration of 25 µg/L.

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	▪ IMPLICATIONS: Characterize with greater detail the true adverse effect that the standard is being developed to prevent, and the relationship to how a drinking water "exceedance" should be interpreted. o Describe the timeline of necessary actions to reduce lead levels below a certain measured value. ▪ Having an understanding of this in terms of implementation is important. For example, assuming that a water supply (or tap) is tested on a regular basis, and that the public (or an individual) is notified in a timely manner, the opportunity for chronic long-term exposure to elevated levels of lead will be greatly reduced. Thus, the exposure is more like that of an acute or sub-chronic exposure. One approach may be to develop guidance that is consistent with US EPA Office of Water values that are developed for specific exposure durations (e.g., 1 day, 10 days, longer-term, and lifetime). These durations are representative of both emergency contamination situations and the reality of some current lead measurements. The guidance should be designed in a manner to determine unreasonable risks to health under the provisions of the Safe Drinking Water Act. ▪ IMPLICATIONS: Characterize the health effects of acute, subchronic, and chronic durations of exposure. • The final approach should be presented in a manner that provides PWS, local officials, and the public with translated and easy to use tools to assist in the interpretation of elevations. Any revisions should be performed in a manner that will provide clear recommendations on the health-based regulation of lead in water. o Another approach may be to develop specific guidance for exceedances at schools. In this guidance, individuals would be assumed to consume only half of the total water consumed at schools. For example, elevations of water lead levels at specific taps often presents very specific exposure scenarios, and very personal questions (i.e., "my child only drinks from a fountain outside of the gymnasium two times per week, is that dangerous?"). Knowing this, an approach that describes how a fraction of the total daily consumption of water (~0.15L), might compare to an estimate derived from consuming all water (~ 0.600L) from one source might be useful. o A hypothetical "heat-map" style approach, using an approximation of the model-based estimates from the EPA approach is shown in the attached Table 1. Note – this table is hypothetical and a stylized representation that should not be interpreted quantitatively. • The approaches could be improved by a detailed analysis of the contribution of environmental media to elevated BLLs. This type of assessment is needed to consider o The previously described CLPPP data or the Adult Blood Lead Epidemiology and Surveillance program data could be more fully explored for this purpose. For

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	example, EPA should explore these sources of data to inform model parameters (and estimates) describing the contribution of all sources to measured levels of blood lead. ▪ For example, a rigorous exploration of clinical outcomes and home lead inspections (of children with blood lead levels over time) may better inform to what extent elevated drinking water concentrations are associated with increased or elevated BLLs. ○ The presented approaches could also be improved by considering how drinking a typical level of water, over various estimates of environmental lead exposure, may change a blood lead level. The change in blood lead levels (ΔBLL; % of increase versus a 0.0 ppb water lead level) over various estimates of total lead uptake could then be considered. ○ This approach would better approximate children with known risk factors, such as minority race/ethnicity; urban residence; residing in housing built before the 1950's; and low family income/poor nutrition. ○ A hypothetical "heat-map" style approach showing how a consideration of measured BLL versus ΔBLL, using estimates from Table 1 (a) [exposures to formula-fed infants] is shown in Tables 2 and 3, respectively. Note – Tables 2 and 3 are hypothetical and stylized representations and should not be interpreted quantitatively. The visualization is presented to show how a determination of "effect" (predicted BLL vs. ΔBLL) is critical, especially as it relates to differences in lead uptake. **Table 1**. A hypothetical "Heat-Map" approach to communicating the risk of elevated blood lead levels (EBLLs) from the chronic consumption of various amounts of water over a continuum of water lead concentrations. (a) Predicted blood lead levels (µg/dL) for **0-6 month old infants** drinking various amounts of water containing 1-45 µg/L of lead.

	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	***20%***	***38%***	***57%***	***76%***	***100%***	***114%***	***133%***	***152%***	***171%***	***190%***	***209%***	***300%***
Water Lead Concentration (µg/L)	1	1.8	1.8	1.9	2.0	2.0	2.1	2.1	2.2	2.2	2.3	2.3	2.6
	4	2.0	2.2	2.4	2.6	2.9	3.0	3.2	3.4	3.7	3.9	4.1	5.1
	5	2.0	2.3	2.5	2.8	3.1	3.3	3.6	3.9	4.1	4.4	4.7	5.9
	10	2.3	2.8	3.3	3.9	4.5	4.9	5.4	6.0	6.5	7.0	7.5	9.9
	15	2.6	3.3	4.1	4.9	5.9	6.5	7.3	8.0	8.8	9.5	10.3	13.8
	16	2.6	3.4	4.3	5.1	6.2	6.8	7.6	8.4	9.2	10.0	10.8	14.5
	20	2.9	3.9	4.9	6.0	7.3	8.0	9.0	10.0	11.0	12.0	13.0	17.5
	25	3.2	4.4	5.7	7.0	8.6	9.5	10.8	12.0	13.2	14.4	15.6	21.0
	30	3.4	4.9	6.5	8.0	9.9	11.0	12.5	13.9	15.3	16.7	18.1	24.3
	35	3.7	5.4	7.3	9.0	11.2	12.5	14.2	15.8	17.4	19.0	20.5	27.5
	40	4.0	6.0	8.0	10.0	12.5	13.9	15.8	17.6	19.4	21.2	22.9	30.6
	45	4.3	6.5	8.8	11.0	13.8	15.3	17.4	19.4	21.4	23.3	25.2	33.4

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(b) Predicted blood lead levels (µg/dL) for **1-2 year old children** drinking various amounts of water containing 1-45 µg/L of lead.

Water Lead Concentration (µg/L)	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	*20%*	*38%*	*57%*	*76%*	*100%*	*114%*	*133%*	*152%*	*171%*	*190%*	*209%*	*300%*
	1	2.2	2.3	2.3	2.4	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.9
	4	2.4	2.5	2.7	2.9	3.1	3.2	3.4	3.6	3.8	3.9	4.1	4.9
	5	2.4	2.6	2.8	3.1	3.3	3.5	3.7	3.9	4.2	4.4	4.6	5.6
	10	2.6	3.1	3.5	3.9	4.5	4.8	5.2	5.7	6.1	6.5	7.0	9.0
	15	2.9	3.5	4.2	4.8	5.6	6.1	6.7	7.4	8.0	8.7	9.3	12.3
	16	2.9	3.6	4.3	5.0	5.8	6.4	7.0	7.7	8.4	9.1	9.7	12.9
	20	3.1	3.9	4.8	5.7	6.7	7.4	8.2	9.1	9.9	10.7	11.6	15.5
	25	3.3	4.4	5.5	6.5	7.9	8.7	9.7	10.7	11.8	12.8	13.8	18.6
	30	3.6	4.8	6.1	7.4	9.0	9.9	11.2	12.4	13.6	14.8	16.0	21.6
	35	3.8	5.2	6.7	8.2	10.1	11.2	12.6	14.0	15.4	16.8	18.2	24.6
	40	4.0	5.7	7.4	9.1	11.2	12.4	14.0	15.6	17.2	18.8	20.3	27.5
	45	4.3	6.1	8.0	9.9	12.3	13.6	15.4	17.2	19.0	20.7	22.4	30.3

(c) Predicted blood lead levels (µg/dL) for **2-6 year old children** drinking various amounts of water containing 1 - 45 µg/L of lead.

Water Lead Concentration (µg/L)	Consumption (L/day)	0.106	0.200	0.300	0.400	0.526	0.600	0.700	0.800	0.900	1.000	1.100	1.580
	Percent of Daily Consumption	*20%*	*38%*	*57%*	*76%*	*100%*	*114%*	*133%*	*152%*	*171%*	*190%*	*209%*	*300%*
	1	2.2	2.2	2.2	2.3	2.3	2.3	2.4	2.4	2.4	2.4	2.5	2.6
	4	2.3	2.4	2.5	2.6	2.8	2.9	3.0	3.2	3.3	3.4	3.6	4.2
	5	2.3	2.4	2.6	2.8	3.0	3.1	3.3	3.4	3.6	3.8	3.9	4.7
	10	2.5	2.8	3.1	3.4	3.8	4.1	4.4	4.7	5.1	5.4	5.7	7.3
	15	2.6	3.1	3.6	4.1	4.7	5.1	5.5	6.0	6.5	7.0	7.5	9.8
	16	2.7	3.2	3.7	4.2	4.9	5.3	5.8	6.3	6.8	7.3	7.8	10.3
	20	2.8	3.4	4.1	4.7	5.6	6.0	6.7	7.3	8.0	8.6	9.2	12.2
	25	3.0	3.8	4.6	5.4	6.4	7.0	7.8	8.6	9.4	10.2	10.9	14.6
	30	3.2	4.1	5.1	6.0	7.2	8.0	8.9	9.9	10.8	11.7	12.7	17.0
	35	3.3	4.4	5.5	6.7	8.1	8.9	10.0	11.1	12.2	13.3	14.3	19.4
	40	3.5	4.7	6.0	7.3	8.9	9.9	11.1	12.3	13.6	14.8	16.0	21.7
	45	3.7	5.1	6.5	8.0	9.7	10.8	12.2	13.6	14.9	16.3	17.6	23.9

Notes

1. The predicted blood levels are shown in the cells shaded green (< 3.75), yellow (>3.75 - 5), orange (>5 - 10), or red (>10) and are reported in µg/dL.
2. Lead uptake (µg/day) was converted to blood lead levels (µg/dL) using coeffficients from a polynomial regression model* derived directly from IEUBK (see polynomial regression coefficients described by Zartarian, et al., 2017 and listed below).
3. In addition to uptake of lead from water, the estimate assumes that:
   - 0-6 month old infant will uptake 3.19 µg of lead per day from diet, soil, and dust.
   - 1-2 year old child will uptake 4.92 µg of lead per day from diet, soil, and dust.
   - 2-6 year old child is exposed to 6.38 µg of lead per day from diet, soil, and dust.

* Blood Pb (µg/dl) = $\beta 0 + \beta 1$ (uptake) + $\beta 2$ (uptake)^2 + $\beta 3$ (uptake)^3 (see polynomial regression coefficients described by Zartarian, et al., 2017 and listed below).

Age Category	Bo	B1	B2	B3
0 - 6 months	0.00786	0.547	-0.0013076	6.00E-06
1-2 year olds	-0.00031	0.447	-0.0006372	1.50E-06
2-6 year olds	0.0008612	0.3342000	-0.0003293	5.20E-07

Table 2. A hypothetical "heat-map" approach to presenting predicted blood lead levels (µg/dL) for 0-6-month old bottle-fed infants, over various estimates of total lead exposure (uptake). Table 2 is based on Table 1(a) estimates of typical water consumption (.526L) by bottle fed infants (i.e., the 100% column in Table 1(a)).

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Water Lead Concentration (µg/L) \ Total Lead Uptake (µg/day)	3.19	4	6	8	10	12	14	16	18	20	21	22
0	1.7	2.2	3.2	4.3	5.3	6.4	7.4	8.4	9.4	10.4	10.9	11.4
1	2.0	2.5	3.5	4.6	5.6	6.7	7.7	8.7	9.7	10.7	11.2	11.7
2	2.3	2.7	3.8	4.9	5.9	6.9	7.9	9.0	10.0	10.9	11.4	11.9
3	2.6	3.0	4.1	5.1	6.2	7.2	8.2	9.2	10.2	11.2	11.7	12.2
4	2.9	3.3	4.4	5.4	6.4	7.5	8.5	9.5	10.5	11.5	11.9	12.4
5	3.1	3.6	4.6	5.7	6.7	7.7	8.7	9.7	10.7	11.7	12.2	12.7
6	3.4	3.9	4.9	5.9	7.0	8.0	9.0	10.0	11.0	12.0	12.5	12.9
7	3.7	4.1	5.2	6.2	7.2	8.3	9.3	10.3	11.3	12.2	12.7	13.2
8	4.0	4.4	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5	13.0	13.4
9	4.3	4.7	5.7	6.8	7.8	8.8	9.8	10.8	11.8	12.7	13.2	13.7
10	4.5	5.0	6.0	7.0	8.1	9.1	10.1	11.0	12.0	13.0	13.5	13.9
11	4.8	5.2	6.3	7.3	8.3	9.3	10.3	11.3	12.3	13.2	13.7	14.2
12	5.1	5.5	6.5	7.6	8.6	9.6	10.6	11.6	12.5	13.5	14.0	14.4
13	5.4	5.8	6.8	7.8	8.8	9.8	10.8	11.8	12.8	13.7	14.2	14.7
14	5.6	6.1	7.1	8.1	9.1	10.1	11.1	12.1	13.0	14.0	14.5	14.9
15	5.9	6.3	7.4	8.4	9.4	10.4	11.4	12.3	13.3	14.2	14.7	15.2
16	6.2	6.6	7.6	8.6	9.6	10.6	11.6	12.6	13.5	14.5	15.0	15.4
17	6.5	6.9	7.9	8.9	9.9	10.9	11.9	12.8	13.8	14.7	15.2	15.7
18	6.7	7.1	8.2	9.2	10.2	11.1	12.1	13.1	14.0	15.0	15.5	15.9
19	7.0	7.4	8.4	9.4	10.4	11.4	12.4	13.3	14.3	15.2	15.7	16.2
20	7.3	7.7	8.7	9.7	10.7	11.7	12.6	13.6	14.5	15.5	16.0	16.4

Table 3. Predicted change (Δ) in BLLs (%) for 0-6-month old infants shown in Table 2. The shading is not health-based and is presented as a visualization tool to contrast the difference between a BLL evaluation (Table 2) and the ΔBLL evaluation here (shading key: green <10; yellow 10-20; orange 20-50, and red >50).

Water Lead Concentration (µg/L) \ Total Lead Uptake (µg/day)	3.19	4	6	8	10	12	14	16	18	20	21	22
0	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1	16%	13%	9%	6%	5%	4%	4%	3%	3%	2%	2%	2%
2	32%	26%	17%	13%	10%	8%	7%	6%	6%	5%	5%	5%
3	49%	39%	26%	19%	15%	13%	11%	9%	8%	7%	7%	7%
4	65%	52%	34%	26%	20%	17%	14%	13%	11%	10%	9%	9%
5	81%	64%	43%	32%	25%	21%	18%	16%	14%	12%	12%	11%
6	97%	77%	51%	38%	30%	25%	22%	19%	17%	15%	14%	13%
7	113%	90%	60%	45%	36%	29%	25%	22%	19%	17%	16%	16%
8	129%	103%	68%	51%	41%	34%	29%	25%	22%	20%	19%	18%
9	145%	115%	77%	57%	46%	38%	32%	28%	25%	22%	21%	20%
10	161%	128%	85%	64%	51%	42%	36%	31%	28%	25%	23%	22%
11	177%	141%	93%	70%	56%	46%	39%	34%	30%	27%	26%	24%
12	192%	153%	102%	76%	61%	50%	43%	37%	33%	29%	28%	27%
13	208%	166%	110%	82%	65%	54%	46%	40%	36%	32%	30%	29%
14	224%	178%	118%	88%	70%	58%	50%	43%	38%	34%	33%	31%
15	240%	191%	127%	95%	75%	62%	53%	46%	41%	37%	35%	33%
16	255%	203%	135%	101%	80%	67%	57%	49%	44%	39%	37%	35%
17	271%	216%	143%	107%	85%	71%	60%	52%	46%	41%	39%	37%
18	286%	228%	152%	113%	90%	75%	64%	55%	49%	44%	42%	40%
19	302%	241%	160%	119%	95%	79%	67%	58%	52%	46%	44%	42%
20	317%	253%	168%	125%	100%	83%	71%	61%	54%	49%	46%	44%

Ryan	In this section, I will focus on improving understanding of variability and uncertainty on the modeling approaches. This type of analysis for Approaches 1 and 2 is most easily effected through a brute-force analysis in which the DW concentration is varied and the

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	effect on BLL calculated. Using an approach similar to the regression above, one could fix the non-drinking water parameters and simply step through scenarios for drinking water. For uncertainly, a similar brute -force approach could be implemented by varying the non-drinking water parameters through either a one-at-a-time variability to establish the marginal effect of each characteristic, or a factorial design experiment where all such parameters are varied at the same time in a systematic fashion that would afford an understanding of the coupled effects of the characteristics. Such methods are well established, but tedious, time-consuming, and computational demanding. An alternative is to write out the full model and take derivatives associated with each parameter in question. One could then do a formal error analysis and determine analytically which parameters are most important in affecting BLL. Here, one would be relying on the detailed analytical model to be a reasonably complete assessment of the variables and parameters needed to describe the relationship between BLL, DW, and the exposure factors accurately. As with any model, the quality of the information obtained from the model is directly related to the quality of the information used to develop the model; garbage in, garbage out. Fortunately, there is a lot of information extant that can be brought to bear on this problem. Such is the point of this entire report. ***My colleagues did not dissuade me from this opinion either nor did they try as this was viewed, I believe universally, as a strategy that is needed and appropriate. In fact, there was strong support for a continued evaluation of the sensitivity of the modeling results to the variation in the parameters in the model. This is especially noteworthy in Approach 3, which has the capability including both variability and uncertainty into the results. It is not clear to me in Approaches 1 and 2 how this might be done in a systematic and mathematically precise manner. In Approach 3, distributional characteristics can be included directly. Further, these distributional characteristics can be separated into population variability and model-parameter and model-specification uncertainty to ascertain where research efforts could indeed produce the most effective use of scientists' time to effect the most useful solution to the problem at hand, namely ascertaining the impact on BLLs in populations under varying drinking water scenarios.***
Vork	Comment: I defer to other experts familiar with the superfund program to draw on analogous approaches for assessing site-specific exposures. • In the California lead in construction standard, where day to day and within day variability in worker exposure can be substantial, pre-emptive protective measures are required for workers assigned to trigger tasks or events. These tasks/events are assumed to result in elevated blood lead levels. Examples of such events may be changes to water systems, water treatment changes and changes in other sources of lead exposure. Then, sample collection during tasks/events designed to obtain a representation of lead in the media of interest (e.g. air in the case of workers and water in the case of household residents) can be obtained and blood lead either modeled or measured can determine whether protective actions are sufficient. In

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	some highly variable exposure conditions, lookup tables or "heat diagrams" have been developed (as described in the June meeting by Dr. Nascarella).

1.6 Additional Comments

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Georgopoulos	***"Supplementary" Reviewer Recommendations:*** I. Though the document under review summarizes quite effectively a very large amount of information, there are occasions where a somewhat informal approach is used to make vague statements concerning important facts. Some examples are: On p. 22: "...the low concentration of outdoor air lead being assumed in this analysis, air lead has a very small effect on overall blood lead values..." On p. 28: "...the selection of input values in the case of soil and dust ingestion rate can have a significant impact on IEUBK model results." On p. 29 "...estimated BLLs were much higher than national averages..." The reader would definitely like to have a better/quantitative understanding of what is a "small effect", a "significant impact," a "much higher" estimate, etc. – a 10% difference can be negligible in one context but unacceptably large in another... It is therefore strongly recommended that statements such as the above are modified to include quantitative characterizations of effect/impact, etc. II. In some cases there are statements that require resolution or correction, e.g. On p. 29 it is stated the USEPA's "EFH does not specify whether the reported central tendency estimate is the arithmetic mean or the geometric mean." One would assume/hope that such an uncertainty can be clarified/resolved within the USEPA. On Pages 58-59 it is stated that "[a] potential limitation of approach 3 is that IEUBK was only used as the basis for an analytical solution and was not used to allow its full capabilities of biokinetic modeling to estimate BLLs." However, the polynomial regression fit of IEUBK that is used in conjunction with SHEDS, in the formal mathematical sense is definitely not an "analytical solution" and should not be identified as such; it is an approximation that can be used the same way an analytical solution would be used. ***References*** Boucher, O., Muckle, G., Jacobson, J. L., Carter, R. C., Kaplan-Estrin, M., Ayotte, P., ... & Jacobson, S. W. (2014). Domain-specific effects of prenatal exposure to PCBs, mercury, and lead on infant cognition: results from the Environmental Contaminants

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	and Child Development Study in Nunavik. *Environmental Health Perspectives, 122(3),* 310. Helsel D. R. (2005). *Nondetects and Data Analysis: Statistics for Censored Environmental Data.* Wiley Interscience. Mushak, P. (2011). Lead and Public Health: Science, Risk and Regulation (Vol. 10). Elsevier. Owen, J. S., & Fiedler-Kelly, J. (2014). *Introduction to Population Pharmacokinetic/Pharmacodynamic Analysis with Nonlinear Mixed Effects Models.* John Wiley & Sons. Saltelli, A., Tarantola, S., Campolongo, F., & Ratto, M. (2004). *Sensitivity Analysis in Practice: A Guide to Assessing Scientific Models.* John Wiley & Sons. Saltelli, A., Ratto, M., Andres, T., Campolongo, F., Cariboni, J., Gatelli, D., ... & Tarantola, S. (2008). *Global Sensitivity Analysis: The Primer.* John Wiley & Sons. Sasso A., Isukapalli S. and Georgopoulos P. (2010). A generalized physiologically-based toxicokinetic modeling system for chemical mixtures containing metals. *Theoretical Biology and Medical Modelling 7 (1): 17.* DOI: 10.1186/1742-4682-7-17. PMCID:PMC2903511. Senut, M. C., Cingolani, P., Sen, A., Kruger, A., Shaik, A., Hirsch, H., ... & Ruden, D. (2012). Epigenetics of early-life lead exposure and effects on brain development. *Future Medicine.* doi.org/10.2217/epi.12.58. Sen, A., Heredia, N., Senut, M. C., Hess, M., Land, S., Qu, W., ... & Ruden, D. M. (2015). Early life lead exposure causes gender-specific changes in the DNA methylation profile of DNA extracted from dried blood spots. *Future Medicine.* doi.org/10.2217/epi.15.2. US EPA (2009). Guidance on the Development, Evaluation, and Application of Environmental Models. EPA/11/K-09/003. Vahter, M., Åkesson, A., Lidén, C., Ceccatelli, S., & Berglund, M. (2007). Gender differences in the disposition and toxicity of metals. *Environmental Research, 104(1),* 85-95. Wang, J. (2015). *Exposure–Response Modeling: Methods and Practical Implementation* (Vol. 84). CRC press. Wainwright, H. M., Finsterle, S., Jung, Y., Zhou, Q., & Birkholzer, J. T. (2014). Making sense of global sensitivity analyses. *Computers & Geosciences, 65,* 84-94.
Goodrum	**Acronyms** ALM = adult lead model

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	AM = arithmetic mean ATSDR = Agency for Toxic Substances and Disease Registry BLL = blood lead level BLRV = blood lead reference value BW = body weight CDC = Centers for Disease Control DW = drinking water EBLL = elevated blood lead level EFH = Exposure Factors Handbook GM = geometric mean GSD = geometric standard deviation ICRP = International Commission of Radiological Protection IEUBK = Integrate Exposure Uptake and Biokinetic model MCA = Monte Carlo Analysis NHANES = National Health and Nutrition Examination Survey µg/dL = micrograms per deciliter **References Cited** California EPA. 2016. Comparison of All Ages Model Version 4 with Leadspread 8 in Evaluation of Lead Exposure at California Hazardous Waste Sites. Poster by K. Gettmann, L. Nakayama Wong, and M. Wade. 2016. Presented at Society of Toxicology Annual Meeting. March 13-17, New Orleans, LA. Available at: http://www.dtsc.ca.gov/AssessingRisk/upload/Final-2016-SOT-Poster-Lead3-09-2016.pdf Goodrum, P.E., G.L. Diamond, J.M. Hassett, and D.L. Johnson. 1996. Monte Carlo modeling of childhood lead exposure: development of a probabilistic methodology for use with the U.S. EPA IEUBK model for lead in children. *Hum. Ecol. Risk Assess.* 2:681–708. Griffin, S., P.E. Goodrum, G.L. Diamond, W. Meylan, W.J. Brattin, and J.M. Hassett. 1999. Application of a probabilistic risk assessment methodology to a lead smelter site. *Hum. Ecol. Risk Assess.* 5(4):845–868. Hogan, K., A. Marcus, R. Smith, and P. White. 1998. Integrated Exposure Uptake Biokinetic Model for Lead in Children: Empirical comparisons with epidemiologic data. *Environ. Health Persp.* 106(Suppl 6):1557-1567. Khoury, G.A. and G.L. Diamond. 2003. Risks to children from exposure to lead in air during remedial or removal activities at Superfund sites: A case study of the RSR lead smelter Superfund site. *J. Exp. Anal. Environ. Epid.* 13:61-65. Lin, C., B. Wang, X. Cui, D. Xu, H. Cheng, Q. Wang, J. Ma, T. Chai, X. Duan, X. Liu, J. Ma, X. Zhang, and Y. Liu. 2017. Estimates of soil ingestion in a population of Chinese children. *Environ. Health Perspect*. https://doi.org/10.1289/EHP930

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	Lorenzana, R.M, R. Troast, J.M. Klotzbach, M.H. Follansbee, G. Diamond. 2005. Issues related to time averaging of exposures to lead. *Risk Anal.* 25(1):169-178. Maddaloni, M., M. Ballew, G. Diamond, M. Follansbee, D. Gefell, P. Goodrum, M. Johnson, K. Koporec, G. Khoury, J. Luey, M. Odin, R. Troast, P. Van Leeuwen, and L. Zaragoza. 2005. Assessing lead risks at non-residential hazardous waste sites. *Hum. Ecol. Risk Assess.* 11:967–1003. McLanahan, E., L. Wilder, K. Scruton, K. Bradham, and R. Worley. 2016. Evaluating the All-Ages Lead Model Using Site-Specific Data: Approaches and Challenges. Presented at Society of Toxicology Annual Meeting. March 13-17, New Orleans, LA. Özkaynak, H., J. Xue, V.G. Zartarian, G. Glen, and L. Smith. 2011. Modeled estimates of soil and dust ingestion rates for children. *Risk Anal.* 31(4):592−608. von Lindern, I., S. Spalinger, M.L. Stifelman, L.W. Stanek, and C. Bartrem. 2016. Estimating children's soil/dust ingestion rates through retrospective analyses of blood lead biomonitoring from the Bunker Hill Superfund Site in Idaho. *Environ. Health Perspect.* 124(9):1462−1470. DOI:44 10.1289/ehp.1510144. USEPA. 1994a. Guidance Manual for the Integrated Exposure Uptake Biokinetic Model for Lead in Children. EPA/540/R-93/081. U.S. Environmental Protection Agency, Washington, DC. USEPA. 1994b. Technical Support Document: Parameters and Equations Used in Integrated Exposure Uptake Biokinetic Model for Lead in Children (v 0.99d). EPA/540/R-94/040. U.S. Environmental Protection Agency, Washington, DC. USEPA. 2001. Risk Assessment Guidance for Superfund (RAGS) Volume 3 - Part A: Process for Conducting Probabilistic Risk Assessment. EPA 540-R-02-002. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC USEPA. 2003. Assessing Intermittent or Variable Exposures at Lead Sites. U.S. Environmental Protection Agency. Office of Solid Waste and Emergency Response. EPA-540-R-03-008. OSWER #9285.7-76. USEPA. 2005. All-Ages Lead Model (AALM) Version 1.05 (External Draft Report). U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC. Archived materials available at https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=139314 White, P., P. Van Leeuwen, B.D. Davis, M. Maddaloni, K.A. Hogan, A.H. Marcus, and R.W. Elias. 1998. The conceptual structure of the Integrated Exposure Uptake Biokinetic Model for Lead in Children. *Environ. Health Persp.* 106(Suppl 6):1513-1530.

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	Zartarian, V., J. Xue, R. Tornero-Velez, and J. Brown. 2017. Children's lead exposure: a multimedia modeling analysis to guide public health decision making. *Environ. Health. Persp.* Manuscript Draft.
von Lindern	**GENERAL COMMENTS** This report represents a substantial effort that should be commended for its thoroughness, rigor and straight-forward, transparent presentation. The methods are fundamentally sound and adherence to appropriate scientific techniques and quality control is evident. If carried forward, with some adjustments, the methodology could be used to provide valuable insight to public health professionals and policy-makers in developing protective health criteria for children using US public water systems. However, EPA states this is only a statistical exercise, but nevertheless is developing a methodology with profound health implications. This makes it difficult to provide specific comments regarding the inputs to, and interpretations of, the output from these models without substantial caveats. There have been some modifications made to the IEUBK analyses that, likely, render the current results spurious for public health or risk assessment. EPA does acknowledge that many of these modifications were made for comparative purposes and do not represent Agency policy; but it is difficult to ignore potential health implications. Moreover, whether the modifications are scientifically defensible, some are in direct conflict with EPA guidance, recommendations, and a history of regulatory decisions. In particular, it should be incumbent on the EPA to resolve how much water the Agency believes US children drink, consumption rates for incidental soil/dust ingestion, inhalation rates, time spent outdoors, etc. Each of the three main pathways (soil/dust, diet, water) have 50%-90% discrepancies in the consumption or intake rates between IEUBK recommendations, Exposure Factors Handbook guidance, and the SHEDS-derived inputs. Having each program select and support which databases and studies will be used in effecting national health protective actions is problematic. If the national databases conflict with EPA policy and practices, then the Agency should resolve the problems and direct the use of the most appropriate data. The Science Advisory Board has had a long and effective record in assisting the Agency in resolving such conflicts. The conflict seems to center around the decision to input the exposure characterization developed for the SHEDS Approach 3 analyses into IEUBK Approaches 1 and 2, where these are both different in magnitude and inappropriate to the development of the IEUBK. The report indicates that this was done for comparative purposes, but it is confusing as to why one would want to compare one model's performance with the inappropriate use of another model; unless it serves to help and rectify the inappropriate data or variable constructs. It seems that in initial comparisons of IEUBK and SHEDS blood lead predictions, EPA assumed over-predictions were due to out-of-date IEUBK default inputs that overestimate the consumption rates and determined to substitute alternatives derived from the SHEDs inputs. Although some updates to the IEUBK are in order and are under review in other committees, this overestimation of blood lead could also be due to simplistic

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	point estimates of soil/dust concentrations that fail to capture the variance in US soil/dust exposures, and drive baseline blood lead levels. Applying the IEUBK across the national population, as accomplished in Approaches 1 and 2, encompasses large variation in several sources, co-factors, and exposure profiles that likely bring the application of the 1.6 gsd of the IEUBK into question when the SHEDS inputs are applied. It is also unclear if the national databases used to develop the SHEDS inputs are reflective of the same populations encompassed in the NHANES surveys. The EPA should also assess and discuss the extent to which the NHANES database captures the US most at-risk populations identified by the CDC and in notable incidents such as the Flint, Michigan crisis. More effective and reliable results might be obtained if Approaches 1 and 2 were developed for exposure stratifications of the national database and at-risk populations, using more appropriate consumption and ingestion rates and soil/dust lead partitions. These stratified results could then be evaluated within variously exposed communities to assess the effectiveness of health benchmark water concentrations. The national picture could be developed and compared to SHEDS Approach 3 by proportionately aggregating the stratified results.
Nascarella	**GENERAL COMMENTS** 1. Overall EPA has described three approaches that are rigorous, credible, and represent a significant body of work to inform the future regulation of lead in drinking water. While there appears to be several opportunities to refine or clarify important aspects of each of the presented approaches, the proposed technical framework is a valuable resource and should be given thoughtful consideration in any future water quality policy deliberations. 2. As presented, the approach lacks sufficient clarity in both how it will be applied to regulating drinking water, and how it should be interpreted from a health-based perspective. Left unchanged, this will serve to add confusion to an already exceedingly difficult conversation about lead in drinking water. Importantly, it will also run counter to the primary goal of this endeavor - an analysis to inform public education requirements, and risk mitigation actions at the household or school level. Any final approach should be presented and performed in a manner that will provide very *clear* communication on the *health-based* regulation of lead in drinking water. 3. No safe level of lead has been identified and all sources of lead exposure should be eliminated. The reviewed document, however, ignores the significant role of deteriorated lead-based paint and the resulting dust and soil contamination as a source of lead exposure responsible for increases in blood lead levels in young children. This concept is not adequately explained or examined in the document and has the potential to divert significant attention away from a very important public health issue – exposure to lead-based paint. 4. The estimate of exposure to lead from water in each scenario requires further explanation. Given this nature of lead release in drinking water supplies, it seems appropriate to better characterize how the exposure model averaging times

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	(biological exposure averaging) account for this, and how the differences in the dose-response relationship of acute exposure (24 hours or less), short-term exposure (1-30 days), and long-term exposure (more than 30 days) are accounted for. Each scenario may present a different type of exposure, associated with a different hazard (or biological effect), and will result in different risks. 5. The IEUBK model seems ill advised for applications where exposure periods are less than three months, or when high exposure occurs less than one per week or varies irregularly. The EPA modeling approaches in the subject document does not seem to be consistent with this application. 6. As regard to the specific application of the approaches, EPA must describe both the risk-based interpretation of blood lead levels (in terms of how they relate to a "critical effect", as defined in a regulatory toxicology context), and very clearly describe how this relates to the regulatory application to a corresponding level of lead in water (in a risk communication context). For example, the described approach does not make clear what an appropriate health-based effect should be? EPA should specifically discuss the risk management rationale to establish this as a "critical effect" and how this relates to a *Health-Based Benchmark*. **REFERENCES** CDC, 2013. CDC's Childhood Lead Poisoning Prevention Program. Available: https://www.cdc.gov/nceh/lead/about/program.htm CDC, 2016. NHANES 2013-2014 Data Documentation, Codebook, and Frequencies. January, 2016. Available: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/PBCD_H.htm CDC, 2012. Measuring childbearing patterns in the United States. https://www.census.gov/newsroom/cspan/childbearing/20120817_cspan_childbearing slides.pdf Johnson K, Posner SF, Biermann J, Cordero JF, Atrash HK, Parker CS, Boulet S, Curtis MG. 2006. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR Recomm Rep. 2006 Apr 21;55(RR-6):1-23. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5506a1.htm Soldin OP, Hanak B, Soldin SJ. Blood lead concentrations in children: new ranges. 2003. Clin Chim Acta 327:109-113.
Vork	**Comment regarding EPA's Background Section of the Charge.** I believe that the working group reports that system-wide action is triggered by an exceedance of 10% of households exceeding the current standard of 15 ug/L. In addition, the working group report indicates that household action would be triggered

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	when individual households exceed some lead concentration in water above the system-wide standard (currently 15 ug/L). **Additional clarifications, limitations and future directions** Add definition of terms for clarity. For example, define historic exposure (exposure leading to an initial blood lead level prior to the exposure time being modeled) versus background exposure (ongoing exposure from non-water sources). Add a discussion of assumptions and assessment of alternate assumptions. For example, an assumption about background exposure to soil and dust was made for the age group 0 – 6 months. Briefly discuss the impact of a different assumption as suggested in the June meeting. In addition, the IEUBK model is calibrated for childhood exposures. If modeling adult women is added to the present effort, an alternate approach and model would be needed. One recommended analysis would be testing the impact of historic (different intensity and chronicity prior to the exposure time being modeled) on the time-to-decay from unacceptable to some determined lower blood lead level for women of childbearing age. Approach 3 results change the current assumption of 20% contribution to blood lead from water. This assumption is used, for example, in California for deriving a public health goal (PHG). Approach 3 provides a data-derived percent of lead exposure from water. If the current assumption of 20% contribution was held constant, what would the levels in other sources need to be to keep blood lead levels below 3.5 and 5 ug/dL? Approaches 1 and 2 With lower levels of lead from widely distributed sources such as ambient air, diet and lead paint - or leaded gas-contaminated soil and dust, lower blood lead levels in the general population would be expected. As a result, more elevated blood lead levels from people exposed to “hot spot” background sources of lead such as contaminated soil from nearby point source emissions, contaminated surfaces in homes and vehicles of lead workers (Hipkins et al. 2004, MMWR 1998, 2008) and nearby uncontrolled lead paint removal projects, may be more detectable from the general population. However, including less frequent but substantially elevated blood lead levels in a regional or national average may mask the effect of those “hot spot” exposures. Hence, more customizable approaches such as 1 and 2 are vital for screening purposes in communities with suspected above average sources of lead exposure or blood lead levels. In addition, saturation kinetics plays a role when frequent spikes followed by very low levels of exposure occur over time. The variability associated with non-national sources and non-constant exposure over time may be greater than the 1.6 GSD currently assigned to exposures in the general population. Approach 3 Results from approach 3 presented to the panel and in a manuscript accepted for publication in EHP illustrate the impact of lead levels in water systems at and below the current system action level of 15 ppb on keeping blood lead below defined levels in defined age groups. This analysis did not apply a factor representing uncertainty. This is a limitation in the approach as presented.

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	Uncertainty factors for specific age groups could be informed by conducting a comprehensive stratified uncertainty analyses as suggested by panel members during the June meeting (see remarks made by Prof. Georgopoulos). Saturation kinetics at very low levels of exposure is subtle and thresholds that indicate a level in which saturation begins in not based on biology (Leggett 1993, OEHHA 2013). Frequent high followed by very low levels of lead exposure changes the kinetics of lead in the human body (Leggett 1993). Recent attempts to limit the frequency as well as intensity of lead intake from contaminated food sources appears (see section 5.2, WHO 2011) in recognition of this effect. Back-calculated water levels leading to specified blood lead levels using the IEUBK model may be higher than a model that incorporates saturation kinetics. This is evident in the effort undertaken in support of updating the worker standard for lead in California (see Table 2 OEHHA 2013). A comparison of back-calculated water levels of lead would be useful to evaluate the impact of frequency and intensity of episodic exposure, predicted blood lead and back-calculated water lead. This comparison is currently a source of uncertainty in the present analysis. **References** Arcus-Arth A, Krowech G, Zeise L, (2005) Breast milk and lipid intake distributions for assessing cumulative exposure and risk, Journal of Exposure Analysis and Environmental Epidemiology, 15, 357-365. Hipkins KL, Materna BL, Payne SF, Kirsch LC, (2004), Family lead poisoning associated with occupational exposure, Clinical Pediatrics, Vol 43. 845-849. Abstract available at http://journals.sagepub.com/doi/10.1177/00099228040430090 9#articleShareContainer MMWR (1998), Occupational and take-home lead poisoning associated with restoring chemically stripped furniture --- California 1998. Available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5013a2.htm MMWR, (2008) Childhood lead poisoning associated with lead dust contamination of family vehicles and child safety seats --- Maine, 2008. Available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5832a2.htm California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2009), Public health goal for lead in drinking water. Available at https://oehha.ca.gov/media/downloads/water/chemicals/phg/leadfinalphg042409_0.pdf California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2013), Estimating workplace air and worker blood lead concentration using an updated physiologically-based pharmacokinetic (PBPK) model, Vork KL, Carlisle JC, Brown JP. ; Available at https://oehha.ca.gov/air/document/oehha-presentation-pbpk-model-blood-lead-and-worker-exposure

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	WHO (2011), Evaluation of Certain Food Additives and Contaminants, Seventy-third meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 960. WHO press Geneva, Switzerland.

Appendix J

ADDITIONAL EPA SENSITIVITY ANALYSES

Draft 6/29/2017

Sensitivity analysis by change input individual by 50% (1 - < 2 years old)

Inputs	Blood Pb Mean (ug/dl) Upper 50%	Blood Pb Mean (ug/dl) Lower 50%	Blood Pb 97.5th (ug/dl) Upper 50%	Blood Pb 97.5th (ug/dl) Lower 50%	Ratio of Upper and Lower Mean	Ratio of Upper and Lower 97.5th
soil Pb concentration	1.45	1.20	4.37	2.84	1.20	1.54
soil ingestion rate	1.44	1.20	4.30	2.94	1.20	1.46
soil absorption rate	1.45	1.20	4.22	2.90	1.21	1.46
dust ingestion rate	1.48	1.18	4.44	3.35	1.26	1.33
dust absorption rate	1.48	1.17	4.22	3.20	1.26	1.32
dust Pb concentration	1.46	1.16	4.09	3.14	1.26	1.30
food absorption rate	1.60	1.02	3.84	3.25	1.57	1.18
food Pb intake	1.60	1.06	4.03	3.45	1.52	1.17
water intake	1.39	1.23	3.88	3.43	1.13	1.13
water absorption rate	1.41	1.23	3.75	3.40	1.14	1.10
air inhalation rate	1.33	1.29	3.70	3.43	1.03	1.08
water Pb concentration	1.42	1.24	3.85	3.62	1.15	1.07
outdoor air Pb concentration	1.36	1.32	3.75	3.57	1.03	1.05
indoor air Pb concentration	1.33	1.32	3.55	3.56	1.00	1.00

Draft 6/29/2017

Sensitivity analysis by change input individual by 50% (0 to 6 months old)

Inputs	Blood Pb Mean (ug/dl) Upper 50%	Blood Pb Mean (ug/dl) Lower 50%	Blood Pb 97.5th (ug/dl) Upper 50%	Blood Pb 97.5th (ug/dl) Lower 50%	Ratio of Upper and Lower Mean	Ratio of Upper and Lower 97.5th
water intake	1.27	0.86	3.58	2.39	1.47	1.50
water absorption rate	1.28	0.88	3.62	2.46	1.46	1.47
water Pb concentration	1.27	0.87	3.63	2.50	1.46	1.45
soil ingestion rate	1.16	0.98	3.21	2.44	1.18	1.32
soil absorption rate	1.14	0.98	3.31	2.52	1.16	1.31
soil Pb concentration	1.14	0.99	3.21	2.59	1.15	1.24
dust ingestion rate	1.17	0.96	3.19	2.69	1.22	1.19
dust Pb concentration	1.16	0.96	3.12	2.63	1.21	1.19
dust absorption rate	1.17	0.95	3.10	2.70	1.24	1.15
food absorption rate	1.18	0.96	3.11	2.71	1.23	1.15
food Pb intake	1.19	0.98	3.19	3.03	1.21	1.05
air inhalation rate	1.09	1.07	3.05	2.96	1.02	1.03
indoor air Pb concentration	1.07	1.09	2.96	3.00	0.98	0.99
outdoor air Pb concentration	1.08	1.07	2.86	2.92	1.00	0.98

Citation of inputs for the two sensitivity tables

- Please check S3 table "in-press" EHP paper we sent for the peer reviews for inputs

Draft 6/29/2017

Inputs	Blood Pb Mean (ug/dl) 1) Upper 50%	2) Lower 50%	Blood Pb 97.5th (ug/dl) 3) Upper 50%	4) Lower 50%	Ratio of Upper and Lower 5) Mean	6) 97.5th
soil Pb concentration						1.54
soil ingestion rate						1.46
soil absorption rate						1.46
dust ingestion rate						1.33
dust absorption rate						
dust Pb concentration						
food absorption rate						
food Pb intake						
water intake						
water absorption rate						
air inhalation rate						
water Pb concentration						
outdoor air Pb concent						
indoor air Pb concentra						

1) Averaged BLL by 50% increase of given input

2) Averaged BLL by 50% decrease of given input

3) 97.5th pcentile BLL by 50% increase of given input

4) 97.5th pcentile BLL by 50% decrease of given input

5) Ratio between averaged BLL between increase and decrease by 50% of given input

6) Ratio between 97.5th BLL between increase and decrease by 50% of given input

Interpretation of two sensitivity tables

- Sensitivity results indicates that inputs of soil/dust pathway is the most sensitive for 1 to <2-year-olds and inputs of water ingestion pathway is the most sensitive for 0- to 6-months infants.