Selection of Concentration-Response Functions Between Lead Exposure and Adverse Health Outcomes for use in Benefits Analysis: Cardiovascular-Disease Related Mortality

Reviewer comments (June 2019) and responses from EPA

Peer Reviewers
- Dr. Deborah Cory-Slechta, University of Rochester
- Dr. Ellen Silbergeld, Johns Hopkins University
- Dr. Howard Hu, University of Washington

Comments from Dr. Cory-Slechta

Review Questions
1. **Overall:**
   a. **Is the document successful in identifying and applying the most relevant studies relating lead exposure to cardiovascular mortality for use in benefits analysis? If not, how can it be improved?**
   b. **Please comment on any changes that would enhance the analysis.**
   c. **Is the document written clearly? Please specify sections in which the clarity can be improved.**

   The description of how relevant studies were identified is somewhat obtuse. For example, it is stated that 8 studies were identified from the EPA ISA and NTP monographs; why were these 8 chosen, was it the totality at the time? Were some excluded that were in those documents, and if so, why were they excluded.
   Additionally, while its obvious why bone Pb value studies were not considered for benefit analysis, it isn't clear why the inclusion criteria were restricted to studies in which blood Pb values were <10 ug/dl only when the intent was to build a concentration-effect function. My interpretation is that it was meant to be consistent with the more current blood Pb concentrations today. However, the findings from higher blood Pbs would seem particularly useful, since additional data and blood lead values would strengthen the function being derived. In addition, it would seem that one could actually compare data (i.e., reductions in blood Pb values) from those blood Pbs> 10 to validate the analyses that were done here. The apparent rationale stated to drive the decision about which health endpoints were considered in this series of reports does nothing to clarify this.
   In general, the document is sufficiently clearly written and understandable.

   RESPONSE: We will revise the text to clarify the identification of studies. Regarding the 8 studies identified from the EPA ISA and NTP monograph, these represent the totality of studies discussed in these documents that estimated the direct association between lead exposure and cardiovascular mortality. Furthermore, to our knowledge, the 8 final studies discussed in our assessment of the literature (some of which were identified through a supplemental literature search using PubMed) represent the totality of studies that estimated the association between blood lead levels and cardiovascular mortality in a US population, were published in a peer-reviewed journal, and had mean blood Pb levels in the study populations less than 10 μg/dL.

Regarding the restriction of studies to those with BLL<10 µg/dL, the intent of this effort is to identify a concentration-response function applicable to current levels of general population lead exposure, which are well below 10 µg/dL. Studies with mean BLL>10 µg/dL could be appropriate to use if they were the only studies available, but they would be much more uncertain regarding effects at levels <5 µg/dL than studies with mean BLL in that range. Further analysis to combine data from across studies (i.e. "build a concentration-effect function") is beyond the scope of this effort. We will reevaluate whether the identified studies with mean BLL>5 µg/dL provide results that are informative regarding the concentration-response function at levels similar to the current US adult population (mean BLL≈1 µg/dL).

2. **Does the document appropriately identify and characterize relevant studies? If not, please describe how it could be improved and identify any studies omitted.**

   I am not aware, nor could I find in searching any specific studies that may have been omitted from the analysis at least with respect to the inclusion criteria stated.
   However, with respect to the issue of 'relevant studies' at large, recognizing that this was the charge posed to this group to carry out, and thus this comment is more likely a question for EPA, it is not clear why such an analysis would be restricted to cardiovascular mortality as a single endpoint, when there is also significant cardiovascular morbidity as well. In fact, if one were parsing, it could be suggested that mortality represents the lowest economic benefit as considered in relation to cardiovascular morbidity, with which one can live a long time with an impaired quality of life. It also isn't clear why each such endpoint would be done in a separate cost-benefit analysis, and if so whether such analyses would be equivalent so that they could ultimately somehow be merged.

   RESPONSE: We will revise the text to add more justification for the decision to focus our resources at this time on the cardiovascular mortality endpoint. Regarding the likely magnitude of economic benefits, we anticipate that the monetized value of reduced risk of cardiovascular mortality would be substantially larger than the monetized value of reduced risk of cardiovascular morbidity for any given change in adult blood lead levels. This result was found in EPA's 1997 Report to Congress, "Benefits and Costs of the Clean Air Act, 1970-1990," which estimated that the value of reduced risk of cardiovascular mortality from lower lead exposure was an order of magnitude higher than the value of reduced risk of hypertension from lower lead exposure. This result occurs because the monetized value of reduced risk of premature mortality far exceeds the monetized value of reduced risk of hypertension using standard economic methods, even though the estimated number of avoided cases of hypertension is much larger than the estimated number of avoided fatalities. That said, we recognize that the risk of hypertension and other cardiovascular morbidity endpoints are likely to be reduced as result of policies that reduce lead exposure. In the future, we do hope to develop approaches to include these effects in regulatory analysis. In order to avoid double counting potential benefits, it would only be appropriate to aggregate the value of reduced non-fatal morbidity risks with the value of reduced mortality risk in a benefits analysis incorporating both endpoints.

3. **The paper defines and applies specific criteria to select key studies to inform the quantitative relationship between Pb and CVD mortality. Are these criteria defined and applied in a scientifically appropriate manner? Should criteria be added, dropped, or modified?**

As noted above, the criteria used for selection of studies from the two monographs is not explicitly stated. If it is the same criteria as for the subsequent papers, it should be explicitly stated. There are also statements that raise questions about selection of studies. For example, p. 6 states: "The quantified dose-response relationships between exposure and health outcomes should be specific to associations with enough evidence to be reasonably associated with the exposure of interest. What is "enough evidence", what is meant by 'reasonably associated' and by whom?

In addition, the focus on blood Pb concentrations only of <10

An additional confusion is generated by the statement (p. 7), "Thus we focus on endpoints with the highest weight of evidence assessments… There is a lack of transparency here.

RESPONSE: We will revise the text to clarify the identification of studies and how health endpoints of lead were selected. For chemicals with formal weight of evidence characterizations available (as is the case with lead), the tiers "causal," "likely causal," and "suggestive of a causal relationship" generally constitute "enough evidence" to consider quantification of health endpoints in regulatory analysis at EPA. Regarding the text on pages 6-7, the sentence following the page 6 quotation indicates that "formal weight of evidence characterizations are available," and references Section 2 of the draft report, which elaborates on the characterizations from the EPA ISA and the NTP lead monograph.

4. **The paper identifies four studies that are determined to be robust and applicable for the purposes of quantifying CVD changes associated with changes in Pb exposure, and derives five concentration-response functions (CRFs) from these studies. Please comment on the derivation of the CRFs relating lead exposure to cardiovascular mortality.**

It is not clear what is meant by the term 'robust' here. The rationale for inclusion/exclusion has issues as noted above and consequently changes again for the purposes of deriving CRFs, yet the rationales for these inclusions, e.g., blood lead as a continuous variable and now blood Pb's <5 ug/dl is never explained except that they would be 'most applicable' for benefits analysis.

The focus on the Aoki study and on a requirement for hematocrit correction is never amply supported. What variables change hematocrit? Age? Sex? Did you correct hematocrit on those bases as well? What's notable in the Aoki study is the 14 year + higher age than included in the Menke et al. or Lanphear et al. studies. Moreover, two of the included studies have no information on age. Age itself is a risk factor for cardiovascular disease, the peak of which differs by age (e.g., Mikkola et al., 2013) raising at least two questions. First, were these considerations included in the benefits analysis CRFs? Secondly, the age range for the Aoki study is much higher than others; could it be that more vulnerable members of the population have already been eliminated in this cohort? Given the absence of information on the age ranges in the other two studies cited, how might this also have influenced the derivation of CRFs?

RESPONSE: We will revise the text to clarify the rationale for inclusion/exclusion of studies. We will clarify that the intent of this effort is to identify concentration-response functions applicable for quantifying to the impacts of marginal changes in blood lead levels relative to current levels of general population lead exposure (adult mean BLL of 0.84 μg/dL in 2013-2014; Tsoi et al. 2016) and consider studies with mean blood lead levels below 5 μg/dL most

informative. We will reevaluate whether the identified studies with mean BLL>5 μg/dL provide results that are informative regarding the concentration-response function at BLL≈1 μg/dL.

The rationale for hematocrit correction is summarized in the report, and further discussion is provided in the Aoki et al. publication. As noted in section 3.2.1, the potential for Pb to cause reduced total red blood cell count (i.e., anemia) could lead to a downward bias in the estimated relationship between blood Pb and CVD mortality because anemia is also a risk factor for CVD mortality. For application of Aoki et al. to an EPA regulatory analysis, it is necessary to determine whether/how to incorporate the hematocrit correction. The report's exploration of methods for doing so clearly includes consideration of age and sex (see Exhibits 24-25).

Models from all four papers adjusted for age of the participants at the time of follow up. Aoki and Ruiz-Hernandez used age as the time scale in the regression analysis, while the Menke and Lanphear included age as a confounder. The Aoki and Ruiz-Hernandez studies include participants who are aged 40 years and older at the time of their NHANES examinations, whereas the Menke and Lanphear studies include participants who are aged 20 years and older at the time of their NHANES examinations. We would not expect the higher age cutoff to represent a risk of selection bias because rates of CVD-M are low before age 40, and NHANES does not screen out participants by health status (e.g. pre-existing cardiovascular morbidity).

5. **Please comment on the use of the five CRFs to estimate incremental health benefits from reduced lead exposure for the general population of US adults.**
   a. **Are all five CRFs equally appropriate for benefits analysis, or should some subset of CRFs be selected for use in benefits analysis (e.g., based on factors such as the range of blood Pb levels, the follow-up period, and the hematocrit correction)?**
   b. **Please comment on the suitability of log-linear or linear functional forms for the CRFs, and how to apply the various tests of functional form presented in the different papers to selection of a function for benefits analysis. Is a particular functional form most defensible for use in benefits analysis?**
   c. **To what age range should the CRFs be applied in benefit analysis? Are there additional considerations or uncertainties that need to be assessed when applying a function to adults under age 40? Do these considerations vary across studies given the differences their underlying data (e.g., functions derived from 1988-1994 blood lead data vs. functions derived from more recent data)?**

Question a is confusing; do you mean the data presented in exhibit 21? They are not explicitly labeled as CRFs. Further, It would be preferable to present these not as lines with no y axis, but on with magnitude of increase on the y axis and blood lead concentration on the x axis, as is the more traditional way to present a concentration effect function. In addition, a z axis should be added that includes age range as appropriate. Restricting these further is not beneficial, indeed addition of as much data as possible to this function would make it more useful.

Based on the way the data is presented in exhibit 21, its difficult to address this question. However, given the non-linearity of effects that have been seen with IQ, it would be relevant to move beyond linear functions. The non-linearity of effects seen with IQ is highly relevant to early studies done with Pb showing non-linearity of its effects (Kern and Audesirk, 2000) with opposite effects on calcineurin depending upon concentration of Pb. This is expected given the calcium-mimetic effects of Pb exposure and with homeostatic effects at low levels of exposure that are overwhelmed at higher exposure concentrations. As such, similar effects might be expected to be seen with cardiovascular function.

As noted above, cardiovascular mortality is clearly related to age, albeit differentially in relation to sex. It would be informative to add additional data to determine whether rates of morbidity by age were higher when blood Pb concentrations of the U.S. population were also higher; this would seemingly add information to the benefit analysis as a type of validation procedure. It is not clear why assessments under age 40 would even be particularly useful given the low incidence at this age range.

RESPONSE: Equation 1 provides the functional form for the concentration response functions and Exhibit 20 lists the parameter estimates to be applied from each of the four studies. We will revise the text to more clearly identify the concentration response functions from each study. In addition, we will consider adding an additional figure that graphically depicts the relationship between blood lead concentration and CVD mortality risk and consider how to incorporate age into the figure. Finally, we will further clarify in the text the basis for the changes in CVDM risk presented in Exhibit 21, including the baseline BLL. The concentration response functions estimated by each of the four studies are log-linear, with steeper effects at lower blood lead concentrations.

We will consider how to provide additional context regarding changes in morbidity and blood Pb concentrations over time. It is not clear, however, how this could be used a validation procedure.

Regarding data from individuals under age 40, the Menke and Lanphear studies included participants who were aged 20 years and older at the time of their NHANES examinations and followed participants for up to 13 years (Menke) or 24 years (Lanphear). However, because of the low baseline incidence of cardiovascular mortality below age 40, we did not apply any of the CRFs to estimate potential changes in CVDM risk resulting from changes in lead exposure among this age group. Based on the reviewer's comment, we will continue to restrict our application of the CRFs to exclude adults under age 40 in a benefits analysis.

6. **Uncertainty exists regarding the Pb exposure level, timing, frequency, and duration contributing to the associations observed between a single adult blood Pb measurement and CVD mortality. There are no available studies with repeated blood lead measurements over time in the same individuals, or that do not rely on biomarkers for lead as a proxy of exposure. The available studies document an association between a one-time measure of adult blood Pb levels and CVD mortality but are not able to assess the association between the full profile of adult Pb exposures over time and CVD mortality directly. This because blood lead is comprised of both recent lead exposure and lead which is mobilized from bone. This creates uncertainty in the extent to which CRFs derived from historic adult blood Pb levels**

would be predictive of CVD mortality in adults with different exposure histories, because on average, blood lead levels have declined over time (see Exhibit 19, years when blood was drawn range from 1988-2010 depending on the study). It is not clear which period of Pb exposure (e.g., childhood, young adulthood, current, lifetime-average, last X years) and what magnitude of exposure during that period drives the observed relationship with CVD mortality.

    a. **Given these considerations*, please comment on the application of CRFs *from historic cohorts to the contemporar*y US adult population and the assumption of no latency period.**
    b. **Please comment on the discussion of potential conceptual models describing the relationship between blood Pb and CVD mortality in Section 5.3. Is one of the conceptual models generally more appropriate for estimating changes in CVD mortality of reduced lead exposure in adults? Is there an alternative conceptual model that would be preferred? Are there conditions when one model might be preferred over others?**
    c. **Does the applicability of the CRFs depend on the duration of the change in lead exposure expected to result from a policy change (e.g., short-term exposure reductions versus chronic exposure reductions)?**

It is not clear that part a) can be answered based on the current available data, since we simply don't know what the critical timing/chronicity of exposure factors are in cardiovascular disease and Pb. From a biological perspective, it seems more likely that cumulative exposure is critical. One could consider a peak exposure being exceeded or intermittent spikes of exposures, but those would be so variable by age across populations that it seems like any health effects could really be diluted out. As noted previously, however, the historic data is extremely useful for more accurately defining blood Pb concentrations of interest given its ability to strengthen the defined relationships, even though based on a single blood Pb measurement. It is difficult to imagine a no latency model as exposure begins in utero and is sustained over the life span at some level in virtually all members of the population.

With respect to the conceptual models, again, the jury is basically out as we don't have the data to substantiate one specific model. From my perspective, model 2 is the best current guess for reasons cited above, but should also be carried out separately by sex, given that both pregnancy and menopause result in significant bone remobilization in women. There is just no data to provide a metric for latency. Moreover, while blood Pb has a half-life of about 30 days, this is certainly not true for bone, where half-life is on the order of decades.

Based on what we understand about the toxicokinetics of Pb, especially half-life of Pb in bone, it would most certainly require that applicability of the CRF would depend upon the duration of the change; one might expect a brief drop in bone Pb with a reduction in Pb exposure, but ultimately, reversing effects may mean clearing out bone Pb stores. This is why you don't see studies of reversal of Pb effects in animal models.

RESPONSE: Based on the reviewer's comment, we will continue to include conceptual model 2 in the report and consider how best to implement this model in regulatory analysis. In the hypothetical application of the concentration response functions in regulatory analysis using

conceptual model 1 that was presented in the report, we estimated age- and sex-specific effects and will continue to do so in applications of any of the other conceptual models.

7. **Does the paper successfully identify and summarize important issues related to uncertainty and variability in the functions and their application? If not, how can it be improved?**
   a. **Are there critical uncertainties that have not been adequately considered?**
   b. **Given these uncertainties, does the approach proposed in the paper generate reasonable confidence in the estimates of the reduction in CVD mortality risk from reduced adult Pb exposure?**

Some uncertainties are discussed, but as mentioned above, the issues of age and sex, which have been shown to modulate cardiovascular mortality, are not incorporated into the analysis in any meaningful way. Incorporation of data sets with blood Pb values that were originally excluded is also likely to strengthen confidence in the estimates of reduction.

RESPONSE: The analysis used age- and sex-specific baseline cardiovascular mortality rates and blood lead levels in its application of the concentration response functions. In addition, all four of the studies adjusted for age and sex in their regression analyses. Menke and Ruiz-Hernandez tested for interactions between BLL and sex, and the interactions were not statistically significant at conventional levels (p > 0.05). Therefore, the analysis did not apply sex-specific hazard ratios in the concentration functions. As noted above, we will consider whether to incorporate additional studies of populations with BLLs > 5 μg/dL.

<u>**Comments from Dr. Silbergeld**</u>

Peer Review Charge Questions

1. **Overall:**

   a. **Is the document successful in identifying and applying the most relevant studies relating lead exposure to cardiovascular mortality for use in benefits analysis? If not, how can it be improved?**

   b. **Please comment on any changes that would enhance the analysis.**

   NO. I must conclude that the use of key studies and a weight of evidence method of evaluating the information in terms of supporting an association between lead and cardiovascular mortality, are not the most transparent, reliable, or comprehensive manner of identifying, evaluating, and extracting relevant data for studies testing the associations between an exposure and an outcome. These are old methods with many problems related to lack of transparency and lack of attention to systematic bias resulting from the arbitrary nature of selecting a limited number of so-called key studies and nontransparent methods of evaluating the reliability of information.

   Ever since the NRC reports* on shortcomings in EPA's methods for reaching decisions on health hazards and risks of toxic substances, the agency has adopted systematic review methods under the leadership of Drs Khris Thayer, Andy Rooney, and others**. As a consequence, this entire analysis should be reconsidered in light of the many problems that have been discussed associated with these older methods.

   We conducted such a systematic review in 2008, which you could update.***

   REFERENCES CITED

   *(NRC (National Research Council). 2014a. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press. NRC. 2014b. Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens. Washington, DC: National Academies Press. NRC. 2014c. Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens. Washington, DC: National Academies Press.)

   ** Morgan, Rebecca L., et al. "GRADE: Assessing the quality of evidence in environmental and occupational health." Environment international 92 (2016): 611-616.

   *** Navas-Acien, Ana, Eliseo Guallar, Ellen K. Silbergeld, and Stephen J. Rothenberg. "Lead exposure and cardiovascular disease—a systematic review." Environmental health perspectives 115, no. 3 (2006): 472-482.

   <u>RESPONSE:</u> *We will revise the text to clarify the identification of studies.*

   We agree with the reviewer concerning the advantages of conducting systematic review. However, our purpose here was not to conduct a hazard assessment and judge the evidence supporting this endpoint; rather it was to identify studies suitable for quantifying changes in cardiovascular disease mortality risk for benefits analysis given the existing hazard assessment. The Agency's Integrated Science Assessment (ISA) for lead was a reasonable starting point for

this exercise given the extensive review of that document through a prescribed process of expert review and public comment.

> c. **Is the document written clearly? Please specify sections in which the clarity can be improved.**

MOSTLY. The document is mostly written clearly although editing might be able to shorten the text. Some of the terms are hard to understand as written. There are some odd statements without justification, such as the statement that "we focus on endpoints with the highest weight of evidence assessments" (7) – why not the greatest increase in odds ratios? Or strongest amount of data from independent studies? Since I have very little trust in weight of evidence based judgments, I find this opaque. Another problematic statement is on p 10, in referring to two of five studies that were reviewed by NTP: "however both studies have limitations that may have biased the results." What are these limitations? How are you defining bias?

RESPONSE: We will revise the text to clarify the reasons for the initial focus on cardiovascular disease mortality, and how the approach described in the current document relates to planned future work on cardiovascular morbidity.

Regarding the question concerning the two studies described as having limitations that may have biased the results: immediately following the quoted passage in the draft report, there is a sentence referring the reader to Appendix A for discussion of the limitations of these studies. To briefly summarize, the cohort used in Weisskopf et al. (2009) suffers from selection bias. When Weisskopf et al. (2015) used methods to address selection bias with the same cohort, they found a significant association between bone lead and cardiovascular mortality. Møller and Kristensen (1992) used older data with blood lead measurements that are likely to be affected by measurement error, which would lead to attenuation bias (though no data on blood lead measurement precision is presented in the study). We define bias as the systematic over- or under-estimation of an underlying effect. It is also worth noting that both studies have relatively small sample sizes compared to NHANES-based studies, yielding less power to detect an underlying effect. We will review the text and consider edits to clarify this point.

2. **Does the document appropriately identify and characterize relevant studies? If not, please describe how it could be improved and identify any studies omitted.**

NO See comments above. This report builds on two reviews, one by EPA and one by NTP, both of which have the shortcomings noted above. This was followed by a limited search of the literature published after these two documents. A short description of search terms and methods was provided. I doubt that the document has identified and utilized all relevant studies.

RESPONSE: Our intent was to be comprehensive in identifying all studies that estimated the association between blood lead levels and cardiovascular mortality in a US population, were published in a peer-reviewed journal, and had mean blood Pb levels in the study populations less than 10 µg/dL. To our knowledge, the 8 studies discussed in our assessment of the literature (identified from a combination of the EPA ISA, the NTP Monograph, a supplemental literature search using PubMed, and a review of the references from all included studies) represent the

*totality of studies that met these criteria at the time the document was written. Further, none of
the three peer reviewers identified any studies of cardiovascular disease mortality meeting these
criteria that had been omitted. We will add information to clarify the extent of the supplemental
search.*

3. **The paper defines and applies specific criteria to select key studies to inform the quantitative
   relationship between Pb and CVD mortality. Are these criteria defined and applied in a
   scientifically appropriate manner? Should criteria be added, dropped, or modified?**

No, I do not support the concept of "key studies" and I think the definition of this term is highly
subjective based on my experience on expert committees at EPA and IARC where it was
customary to use this method for assessing hazards. This is a major argument in favor of the
greater transparency of systematic approaches. More fundamentally, the goal of such reviews
should be to examine the entirety of the relevant literature and then to assess these studies
using clear methods and a priori criteria to extract a consistently evaluated set of data.

*RESPONSE: The "key studies" were all studies that satisfied clearly stated inclusion criteria.
Exhibits 3, 4, and 18 transparently display the path from which the initial set of 15 studies was
narrowed to 4 studies. All reasons for exclusion were clearly stated, applied equally to all
studies, and were related only to the utility of the studies in providing an estimated
concentration-response function applicable to current general population blood lead levels. No
studies were excluded on the basis of any other consideration, such as results of the studies or
any judgments related to study quality. Exhibits 18-21 demonstrate extraction of a consistently
evaluated set of data. However, we will reevaluate whether the identified studies with mean
BLL>5 µg/dL provide results that are informative regarding the concentration-response function
at levels similar to the current US adult population (mean BLL≈1 µg/dL).*

4. **The paper identifies four studies that are determined to be robust and applicable for the
   purposes of quantifying CVD changes associated with changes in Pb exposure and derives five
   concentration-response functions (CRFs) from these studies. Please comment on the
   derivation of the CRFs relating lead exposure to cardiovascular mortality.**

Relying on a small number of studies is the problem: you are only assessing four papers [and
one highly relevant paper, by Menke, was excluded because it was similar to another paper --
having similar but independently conducted studies is very useful in increasing confidence in the
analysis and reducing concerns about systematic bias. Not sure what you mean by "robust" in a
process using only 4 references. Ideally, your CRFs would be based on a meta-analysis based on
a systematic review of the literature.

*RESPONSE: The 4 identified "key studies" are the only studies that met the criteria developed to
identify those studies estimating concentration-response functions most applicable for EPA
regulatory analysis. The paper by Menke et al. is not excluded; it is one of the 4 "key studies" for
which the draft report presents a concentration-response function (see Exhibits 18-21). The 4
key studies are "similar but independently conducted studies" and we agree that this "is very
useful in increasing confidence in the analysis and reducing concerns about systematic bias."*

Meta-analysis is a very useful tool for combining data from separate independent studies; we judged it to be inapplicable in this instance because the 4 studies are all from NHANES and have overlapping cohorts.

5. **Please comment on the use of the five CRFs to estimate incremental health benefits from reduced lead exposure for the general population of US adults.**

   a. **Are all five CRFs equally appropriate for benefits analysis, or should some subset of CRFs be selected for use in benefits analysis (e.g., based on factors such as the range of blood Pb levels, the follow-up period, and the hematocrit correction)?**

NO. Your decision to exclude papers with populations whose range of blood lead levels exceeds 10 ug/dL makes no sense whatsoever. As long as the study includes persons with PbB<10, it is possible to extract useful information what you call CRFs. The follow up is also only relevant for prospective or retrospective studies. Cross sectional studies can be very valuable. If you had more studies, you could run a test to see how important the so-called hematocrit correction is in terms of affecting the analysis. This has become less important after the studies on red cell and plasma lead as biomarkers for lead toxicity*

> REFERENCE CITED
>
> *Rosen, John F., C. Zarate-Salvador, and Emma E. Trinidad. "Plasma lead levels in normal and lead-intoxicated children." *The Journal of pediatrics* 84.1 (1974): 45-48.

RESPONSE: Regarding the restriction of studies to those with BLL<10 µg/dL, the intent of this effort is to identify a concentration-response function applicable to current levels of general population adult lead exposure, which are well below 10 µg/dL. Studies with mean BLL>10 µg/dL could be appropriate to use if they were the only studies available, but they would be much more uncertain regarding effects at levels <5 µg/dL than studies with mean BLL in that range. Further analysis to combine observation-level data from across studies is beyond the scope of this effort. We will reevaluate whether the identified studies with mean BLL>5 µg/dL provide results that are informative regarding the concentration-response function at levels similar to the current US adult population (mean BLL≈1 µg/dL).

We did not exclude cross-sectional studies. However, we did not identify any cross-sectional studies of the association between blood lead and cardiovascular mortality in US populations.

The rationale for hematocrit correction is summarized in the report, and further discussion is provided in the Aoki et al. publication. Aoki et al. provided extensive analysis comparing models with and without hematocrit correction and adjustment and discussed why the models including the correction were preferable. No other studies are available that consider the hematocrit correction in modeling Pb and cardiovascular mortality.

   b. **Please comment on the suitability of log-linear or linear functional forms for the CRFs, and how to apply the various tests of functional form presented in the different papers to selection of a function for benefits analysis. Is a particular functional form most defensible for use in benefits analysis?**

This is a question of methods. Log-linear analysis is often done with lead and other environmental exposures because these are almost always non-normal in distribution, that is, usually skewed to the left as evident in all the NHANES data. Since the outcome measure is not skewed, it is useful to use log-linear conversions. In terms of using choices in using continuous or stratified variables depends upon the statistical modeling. The use of quintiles and splines can be very informative.

RESPONSE: Thank you.

     c.   **To what age range should the CRFs be applied in benefit analysis? Are there additional considerations or uncertainties that need to be assessed when applying a function to adults under age 40? Do these considerations vary across studies given the differences their underlying data (e.g., functions derived from 1988-1994 blood lead data vs. functions derived from more recent data)?**

I think you are confusing something here. Cardiovascular mortality and diseases are age related and thus it is appropriate to examine an age range in which cardiovascular mortality is expected to occur. Some analyses have in fact examined whether lead exposure shifts the expected age-related patterns to younger aged persons. I don't see how the timing of the NHANES data is involved in this question since many of your so a-called key studies are not based on NHANES.

RESPONSE: All four of our "key studies" are based on NHANES. The Menke and Lanphear studies rely on NHANES III, Ruiz-Hernandez uses NHANES III and continuous NHANES (1999-2004), and Aoki uses continuous NHANES (1999-2010).

Regarding age, the Menke and Lanphear studies included participants who were aged 20 years and older at the time of their NHANES examinations and followed participants for up to 13 years (Menke) or 24 years (Lanphear). However, because of the low baseline incidence of cardiovascular mortality below age 40, we did not apply any of the CRFs to estimate potential changes in CVDM risk resulting from changes in lead exposure among this age group. Based on this and other reviewer comments, we will continue to restrict our application of the CRFs to exclude adults under age 40 in a benefits analysis.

6. **Uncertainty exists regarding the Pb exposure level, timing, frequency, and duration contributing to the associations observed between a single adult blood Pb measurement and CVD mortality. There are no available studies with repeated blood lead measurements over time in the same individuals, or that do not rely on biomarkers for lead as a proxy of exposure. The available studies document an association between a one-time measure of adult blood Pb levels and CVD mortality but are not able to assess the association between the full profile of adult Pb exposures over time and CVD mortality directly. This because blood lead is comprised of both recent lead exposure and lead which is mobilized from bone. This creates uncertainty in the extent to which CRFs derived from historic adult blood Pb levels would be predictive of CVD mortality in adults with different exposure histories, because on average, blood lead levels have declined over time (see Exhibit 19, years when blood was drawn range from 1988-2010 depending on the study). It is not clear which period of Pb exposure (e.g., childhood, young adulthood, current, lifetime-average, last X years) and what**

magnitude of exposure during that period drives the observed relationship with CVD mortality.

Many of the studies of lead exposure and CVD outcomes have utilized coetaneous measurements of blood lead (e.g., the blood pressure studies). Bone lead is used as a marker of cumulative including earlier lead and because of the imprecision of the method, it is not useful for characterizing low level exposures. As far as we know {based on a study we have done of adolescents), cardiovascular function in children (including blood pressure and heart rate variability measures), there is no association between blood lead and alterations in cardiovascular function. We do not have information on the possible associations between early lead exposure and later cardiovascular disease. There may be some early life effects of lead on kidney function that may have impacts on cardiovascular outcomes later in life.

RESPONSE: Thank you.

a. **Given these considerations, please comment on the application of CRFs _from historic cohorts to the contemporary_ US adult population and the assumption of no latency period.**

I do not think there is a "latency period" for lead and cardiovascular outcomes based on what we know of mechanisms.* Mortality may be delayed because of the age-relatedness of death due to cardiovascular failure, which is why I advise inclusion of all endpoints relevant to cardiovascular disease including those that increase risks of mortality (see general comments). To the extent that kidney function is an important cofactor, early lead exposure can impair the development of this organ with delayed effects including chronic kidney disease. The release of lead from bone during menopause in women may be a delayed effect, but the impact on blood pressure is not delayed as it closely linked to the rate of bone mineral loss.**

REFERENCES CITED

*Vaziri, N. D., & Sica, D. A. (2004). Lead-induced hypertension: role of oxidative stress. Current hypertension reports, 6(4), 314-320.

**Nash, D., Magder, L., Lustberg, M., Sherwin, R. W., Rubin, R. J., Kaufmann, R. B., & Silbergeld, E. K. (2003). Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. _Jama_, _289_(12), 1523-1532.

RESPONSE: Given that the reviewer mentions multiple mechanisms by which cardiovascular effects of lead exposure may be delayed, we will consider developing conceptual model 2 (in addition to retaining conceptual model 1) for potential application in regulatory analysis.

b. **Please comment on the discussion of potential conceptual models describing the relationship between blood Pb and CVD mortality in Section 5.3. Is one of the conceptual models generally more appropriate for estimating changes in CVD mortality of reduced lead exposure in adults? Is there an alternative conceptual model that would be preferred? Are there conditions when one model might be preferred over others?**

The models are not very persuasive given the paucity of data.

RESPONSE: Given the paucity of data, we will continue to develop and present applications consistent with multiple conceptual models relating lead exposure to cardiovascular mortality.

    c.   Does the applicability of the CRFs depend on the duration of the change in lead exposure expected to result from a policy change (e.g., short-term exposure reductions versus chronic exposure reductions)?

Not sure what you mean. We can impute the size of increases in odds at lower levels of blood lead from well conducted studies. However, we have evidence that the effects of lead on blood pressure at low exposures have a greater effect rate than effects at higher doses, so using linear imputation may be erroneous. We have not determined the so-called "no effect" level for lead and blood pressure. Why do you think there will be a policy change to lower lead exposures?

RESPONSE: The EPA has the statutory authority to propose and issue regulations to lower lead exposures from a variety of media. The intent of this document is to develop an approach to quantify potential changes in adult cardiovascular mortality that could result from any such regulations. Some regulatory authorities relate to transient or intermittent increases in lead exposure (e.g., Lead Renovation, Repair, and Painting program), while others relate to chronic lead exposure (e.g., lead in drinking water).

7. **Does the paper successfully identify and summarize important issues related to uncertainty and variability in the functions and their application? If not, how can it be improved?**

    a.   Are there critical uncertainties that have not been adequately considered?

    b.   Given these uncertainties, does the approach proposed in the paper generate reasonable confidence in the estimates of the reduction in CVD mortality risk from reduced adult Pb exposure?

You do not have enough data to even start to understand uncertainty and variability. That's why relying on a few key studies and excluding similar studies is not advisable.

RESPONSE: The four identified "key studies" are the only studies that met the criteria developed to identify those studies estimating concentration-response functions most applicable for EPA regulatory analysis. We are not aware of other studies meeting these criteria that were excluded.

GENERAL COMMENTS from Dr. Silbergeld:

The decision to focus solely on cardiovascular mortality, omitting all the other outcomes of lead effects on cardiovascular function, including those that are predictors of premature cardiovascular mortality (as noted in the NTP review), severely limits the value of this exercise. Using death as the sole endpoint is rather like the LD50 studies that were done in animal toxicology. Since our goal is to prevent cardiovascular mortality, we are guided by the incidence of more sensitive endpoints that are relevant to and predictive of increased risks of death such as hypertension, stroke, atherosclerosis, renal dysfunction – in fact, all the endpoints discussed

in the NTP report. This decision to limit your analysis to death also prevents a more complete assessment of benefits to include health care costs for treating the non-death outcomes, as well as the standard measures of DALYs, QALYs, and other measures of considerable socioeconomic importance.

The use of outmoded methods – key studies, nonsystematic searching of the literature, nontransparent evaluation methods – has severely limited this analysis.

RESPONSE: We will revise the text to add more justification for the decision to focus our resources for extending benefits analysis of lead health effects at this time on the cardiovascular mortality endpoint. A major reason is that we anticipate that the monetized value of reduced risk of cardiovascular mortality would be substantially larger than the monetized value of reduced risk of cardiovascular morbidity for any given change in adult blood lead levels. This result was found in EPA's 1997 Report to Congress, "Benefits and Costs of the Clean Air Act, 1970-1990," which estimated that the value of reduced risk of cardiovascular mortality from reduced lead exposure was an order of magnitude higher than the value of reduced risk of hypertension from reduced lead exposure. This result occurs because the monetized value of reduced risk of premature mortality far exceeds the monetized value of reduced risks of hypertension and subsequent non-fatal effects using standard economic methods, even though the estimated number of avoided cases of hypertension is much larger than the estimated number of avoided fatalities. That said, we recognize that hypertension and other cardiovascular morbidity endpoints are likely to be avoided as result of policies that reduce lead exposure. In the future, we do hope to develop approaches to include these effects in regulatory analysis.

Comments from Dr. Hu

Review Questions
1. **Overall:**

a. **Is the document successful in identifying and applying the most relevant studies relating lead exposure to cardiovascular mortality for use in benefits analysis? If not, how can it be improved?**

b. **Please comment on any changes that would enhance the analysis.**

c. **Is the document written clearly? Please specify sections in which the clarity can be improved.**

Overall, the document is very clearly written, the conceptual basis is strong, the studies selected are appropriate, the analyses and modeling conducted are appropriate and clear, and the interpretation (including range of possible interpretations based on differing assumptions) is mostly correct.

I do have several observations and suggestions, however, that I will list here and that will be repeated below given the overlapping nature of the peer review charge questions posed.

A. In terms of the studies selected for this analysis, the criteria applied for selecting the Key Studies for derivation of the concentration response function (section 4.1) are, in my view, a bit too strict. Instead of requiring both a mean blood lead below 5 ug/dL and a "relatively large sample size", it would seem also useful to include a study with a "relatively large sample size" that has an "adequately" sized sub-population of subjects with blood lead below 5 ug/dL (i.e., the mean blood of the entire sample may be 5 or greater, but analyses can be made of a fairly large sized sub-sample with blood leads under 5), as it would potentially serve the same purpose. From this perspective, for example, it may still be useful to look at Weisskopf et al. (2015), since, given the mean blood lead was 5.5 ug/dL, it probably has a fairly substantial sub-population of subjects with blood leads <5 ug/dL.

RESPONSE: We will reevaluate whether the identified studies with mean BLL>5 µg/dL provide results that are informative regarding the concentration-response function at levels similar to the current US adult population (mean BLL≈1 µg/dL).

B. A conceptual aspect of the lead exposure-cardiovascular disease relationship that appears to be missing is acknowledgment of the fact that lead exposure (at blood leads <10) is now known as a risk factor for hypertension (with the evidence for causality judged as sufficient by the EPA and NTP, as reviewed in the document, Section 2.2); and hypertension, in turn, is known as a major risk factor for cardiovascular mortality. In addition, as discussed in the document (Section 2.3) it is clear that lead's impact on cardiovascular disease (and, in turn, cardiovascular mortality), has other likely mechanistic pathways, such as disruption of endothelial lining, growth and repair and direct impacts on the heart. Thus, a level of analysis that should be applied in examining studies of low-level lead exposure and cardiovascular mortality is determining whether, for example, blood pressure or hypertension was controlled for in the analyses. If so, it could be argued that the analysis is "over-controlling", since it is removing from the impact of lead exposure any effect on blood pressure or hypertension. Ideally, a complete analysis would report results of blood lead's association with CV mortality both with and without hypertension

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in the model (and/or applying a statistical approach to disentangling the relative impacts of the two possible pathways, such as structural equation modeling).

RESPONSE: We will revise the text to make clear that hypertension is a potential intermediary in the relationship between lead exposure and cardiovascular mortality. Out of the four studies we identified for application of a concentration-response function, three of them (Menke, Ruiz-Hernandez, and Lanphear) control for hypertension in the analysis. Inclusion of hypertension in the model could lead to a downward bias on the estimated effect of blood lead on mortality. Aoki does not control for hypertension. Because none of these studies report results that both do and do not control for hypertension (while controlling for all other potential confounders), it is not possible to directly compare effect size estimates across the two approaches to disentangle the effect of hypertension on mortality from other mechanisms affecting cardiovascular mortality without additional analysis that would be beyond the scope of this effort.

C. In Section 2.3.5 "Summary", I suggest adding the words (highlighted in green) in the following sentence: "As discussed in Section 5.3, Pb in the body may be a result of recent exposures (i.e., within the last 30 days) or endogenous exposures due to re-release of Pb from bone (or the result of chronic exposure and cumulative effects)". It is critical to acknowledge, here and elsewhere in the document, that the most likely reason why bone lead acts like a biological marker that predicts CV mortality and other adverse outcomes better than blood lead is because it reflects chronic exposure and cumulative impacts over many years. In my opinion, this mechanism is more likely than bone lead serving as an endogenous source of lead, since if the latter were true, blood lead levels would still theoretically serve as a superior biomarker.

RESPONSE: We will revise the text to include the reviewer's suggested language and to acknowledge this point elsewhere in the document.

D. In section 3.1 (Identification of Potential Key Studies), I have an issue with the statement "Given that the majority of the evidence relating Pb exposure to CVD mortality is based on blood Pb levels as the biomarker, and that the well-accepted pharmacokinetic models (e.g., Leggett, 1993; U.S. EPA, 1996) have limited capability to predict and validate bone Pb levels, in this analysis we concentrate solely on studies using blood Pb as the biomarker of exposure." A study that is potentially important to the entire exercise conducted in this document is Park et al., 2009[1], which provides an approach for estimating bone lead levels (a measure of cumulative lead exposure) in NHANES and then applies the approach to examining the association of lead with blood pressure in NHANES, finding that the predicted bone lead variable has a stronger association with blood pressure than the measured blood lead (full disclosure: I was a collaborator and co-author on this study). Given the recent NHANES studies on lead and mortality reviewed in this document (Lanphear et al, Ruiz-Hernandez et al., Aoki et al.), it would seem potentially instructive to apply this approach to predicting bone lead and using this biomarker to re-estimate the impact of lead on CV mortality. (I have recently discussed this with Professor Sungkyun Park, the first author of Park et al., 2009, and he is considering this project). Perhaps more to the point, since the mandate of this document does not include primary re-

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[1] Park SK, Mukherjee B, Xia X, Sparrow D, Weisskopf MG, Nie H, Hu H. Bone lead level prediction models and their application to examine the relationship of lead exposure and hypertension in the Third National Health and Nutrition Examination Survey. J Occup Environ Med. 2009 Dec;51(12):1422-36. doi: 10.1097/JOM.0b013e3181bf6c8d. PubMed PMID: 19952788; PubMed Central PMCID: PMC2939477.

analyses of NHANES or other data, the authors should consider discussing how the CRF's could change if one was able to apply a marker of lead exposure that was more specific for cumulative lead exposure than blood lead levels. They do discuss the limitation inherent in blood lead levels that is associated with the inability to distinguish acute lead exposure from lead that is mobilized from bone stores accumulated over many years, but they do not go further to discuss how this might be addressed by adopting a strategies to estimate cumulative exposure (such as discussed above).

RESPONSE: The reviewer correctly notes that primary re-analysis of the data falls outside the scope of this effort. However, we would consider any future studies in the peer-reviewed literature that relate other biomarkers of lead exposure, including bone Pb, to cardiovascular mortality as potentially applicable to regulatory analysis. We will revise the text to note that analysis of bone Pb could be potentially relevant to this effort. Regarding strategies to address cumulative lead exposure, we will continue to include conceptual model 2 in the report and consider how best to implement this model in regulatory analysis.

E. In Section 5.2, there is a discussion of the level of detection (LOD) in blood lead in NHANES. This is appropriate, given the importance of LOD as a factor in these studies in which the mean blood lead levels are very close to the LOD. It is probably worth noting that since the 2013-2014 cycle the LOD for blood lead in NHANES (as measured by the CDC's lab) has been 0.07 ug/dL (i.e., much lower than the LOD's discussed in Section 5.2) since the lab switched to ICP-MS and upgraded methods to reduce contamination[2].

RESPONSE: None of the studies we identified used data from NHANES 2013-3014 or later. However, we will revise the text to note that the level of detection of lead in blood in NHANES has continued to decline.

F. In Section 5.3, the document states "…we do not recommend using bone Pb to predict CVD mortality in benefits analysis. This is because of the uncertainties in modeling bone Pb levels with available PBPK models, and that the fact that currently only Weisskopf et al. (2009, 2015) has evaluated the relationship between bone Pb and CVD mortality risk. Therefore, we have opted not to present the potential bone Pb conceptual models in this report." However, there have been a number of studies relating bone lead levels to risk of hypertension (for example, Hu

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[2] Caldwell KL, Cheng PY, Jarrett JM, Makhmudov A, Vance K, Ward CD, Jones RL, Mortensen ME. Measurement Challenges at Low Blood Lead Levels. *Pediatrics*. 2017 Aug;140(2):e20170272. doi: 10.1542/peds.2017-0272. Epub 2017 Jul 17. PubMed PMID: 28771411; PubMed Central PMCID: PMC5709716

et al., 1996[3]; Korrick et al, 1999[4]; Cheng et al, 2001[5],Martin et al., 2006 [6]), and hypertension, as noted earlier, is a major risk factor for CV disease. So it would be entirely possible and appropriate to model bone lead (or estimated bone lead) as a risk factor for hypertension, and then use established CRF's of hypertension/blood pressure to then model risks for CV mortality. This is, in fact, the method that the Global Burden of Disease has used to model lead's impact on mortality and disability-adjusted life years world-wide[7].

RESPONSE: Our goal is to estimate the change in cardiovascular mortality associated with changes in lead exposure. We recognize the potential value of an approach based on relating bone lead levels to hypertension, and then hypertension to cardiovascular mortality. We have greater confidence in estimates that directly estimate the association between measures of lead exposure and cardiovascular mortality but will further consider this alternative. We will also consider models of hypertension in our future work on cardiovascular disease morbidity.

G. Section 5.3. This is an important section that has been, for the most part, well-thought out and drafted.

    a. With regards to Conceptual Model 1, I think it would be useful to point out that a critically important practical implication of the uncertainty discussed is that we don't know if a population with BLLs in the 0-5 ug/dL from recent low-level exposures (i.e., naïve to historical exposures, such as a population of young US adults who are experiencing low-level lead exposure from an industrial source) will have the same risks of CVD as a population with BLLs in the 0-5 ug/dL that originate from lead mobilized from bone that had accumulated from many years/decades of exposure (e.g., US adults older than 50, who have relatively high bone lead stores from exposure to combusted leaded gasoline).

    b. With regards to Conceptual Models 2 and 3 and the metric involving "average blood Pb over x years", very few populations have yearly blood lead levels measured over years (with the exception of workers exposed to lead and subject to the OSHA lead standard). However, there are cohort studies in which whole blood samples were collected and

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[3] Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A. The relationship of bone and blood lead to hypertension. The Normative Aging Study. JAMA. 1996 Apr 17;275(15):1171-6. Erratum in: JAMA 1996 Oct 2;276(13):1038. PubMed PMID: 8609684.

[4] Korrick SA, Hunter DJ, Rotnitzky A, Hu H, Speizer FE. Lead and hypertension in a sample of middle-aged women. Am J Public Health. 1999 Mar;89(3):330-5. PubMed PMID: 10076481; PubMed Central PMCID: PMC1508610.

[5] Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. Am J Epidemiol. 2001 Jan 15;153(2):164-71. PubMed PMID: 11159162.

[6] Martin D, Glass TA, Bandeen-Roche K, Todd AC, Shi W, Schwartz BS. Association of blood lead and tibia lead with blood pressure and hypertension in a community sample of older adults. Am J Epidemiol. 2006 Mar 1;163(5):467-78. Epub 2006 Jan 18. PubMed PMID: 16421242.

[7] GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1923-1994. doi: 10.1016/S0140-6736(18)32225-6. Epub 2018 Nov 8. PubMed PMID: 30496105; PubMed Central PMCID: PMC6227755.

archived every few years (that could be measured for blood lead), in which case it would be useful to apply the "cumulative blood lead index" as the method for estimating cumulative lead exposure, which, in turn, has been shown to be highly correlated with bone lead[8].

RESPONSE: We will incorporate the reviewer's comments about conceptual model 1 and the nature of the uncertainty into the text. We also recognize the value in the reviewer's suggestion to examine the association between cardiovascular mortality and a cumulative blood lead index and will further consider this alternative.

2. Does the document appropriately identify and characterize relevant studies? If not, please describe how it could be improved and identify any studies omitted.

See my comments in 1.A and 1.D above.

RESPONSE: Thank you.

3. The paper defines and applies specific criteria to select key studies to inform the quantitative relationship between Pb and CVD mortality. Are these criteria defined and applied in a scientifically appropriate manner? Should criteria be added, dropped, or modified?

See my comments in 1.A. and 1.F above.

RESPONSE: Thank you.

4. The paper identifies four studies that are determined to be robust and applicable for the purposes of quantifying CVD changes associated with changes in Pb exposure, and derives five concentration-response functions (CRFs) from these studies. Please comment on the derivation of the CRFs relating lead exposure to cardiovascular mortality.

Appropriate, from my perspective.

RESPONSE: Thank you.

5. Please comment on the use of the five CRFs to estimate incremental health benefits from reduced lead exposure for the general population of US adults.

    a. **Are all five CRFs equally appropriate for benefits analysis, or should some subset of CRFs be selected for use in benefits analysis (e.g., based on factors such as the range of blood Pb levels, the follow-up period, and the hematocrit correction)?**

They each have strengths and limitations that, in my opinion, don't warrant excluding or disproportionate weighting.

RESPONSE: Thank you.

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[8] Hu H, Shih R, Rothenberg S, Schwartz BS. The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ Health Perspect. 2007 Mar;115(3):455-62. Epub 2006 Dec 22. Review. PubMed PMID: 17431499; PubMed Central PMCID: PMC1849918.

b. **Please comment on the suitability of log-linear or linear functional forms for the CRFs, and how to apply the various tests of functional form presented in the different papers to selection of a function for benefits analysis. Is a particular functional form most defensible for use in benefits analysis?**

I am supportive of the approach taken in the document, and otherwise do not have the statistical expertise to comment on the details of the methodology.

RESPONSE: Thank you.

c. **To what age range should the CRFs be applied in benefit analysis? Are there additional considerations or uncertainties that need to be assessed when applying a function to adults under age 40? Do these considerations vary across studies given the differences their underlying data (e.g., functions derived from 1988-1994 blood lead data vs. functions derived from more recent data)?**

I do believe, as implied in these questions, that both age range and secular period of the observations need to be taken into account. Ideally, the studies (and data) can be analyzed to compare the effect estimates of the same age range over different time periods. This is important given that blood lead levels in the same age range but over different secular time periods will likely represent different lead burdens given secular trends in lead exposure in the US and the mobilization of lead from stores accumulated in bone. In other words, within a specific age group, blood lead levels taken in the 1980's early 1990's will likely proportionately reflect more lead from acute exposures v. lead mobilized from bone, whereas blood lead levels from the 200's will likely proportionately reflect more lead mobilized from bone v. acute exposures. These differences, in turn, may have differential impacts on cardiovascular outcomes.

RESPONSE: Thank you.

6. Uncertainty exists regarding the Pb exposure level, timing, frequency, and duration contributing to the associations observed between a single adult blood Pb measurement and CVD mortality. There are no available studies with repeated blood lead measurements over time in the same individuals, or that do not rely on biomarkers for lead as a proxy of exposure. The available studies document an association between a one-time measure of adult blood Pb levels and CVD mortality but are not able to assess the association between the full profile of adult Pb exposures over time and CVD mortality directly. This because blood lead is comprised of both recent lead exposure and lead which is mobilized from bone. This creates uncertainty in the extent to which CRFs derived from historic adult blood Pb levels would be predictive of CVD mortality in adults with different exposure histories, because on average, blood lead levels have declined over time (see Exhibit 19, years when blood was drawn range from 1988-2010 depending on the study). It is not clear which period of Pb exposure (e.g., childhood, young adulthood, current, lifetime-average, last X years) and what magnitude of exposure during that period drives the observed relationship with CVD mortality.

a. **Given these considerations, please comment on the application of CRFs from historic cohorts to the contemporary US adult population and the assumption of no latency period.**

I agree with these concerns, as I discussed in various ways above.

RESPONSE: Thank you.

b. **Please comment on the discussion of potential conceptual models describing the relationship between blood Pb and CVD mortality in Section 5.3. Is one of the conceptual models generally more appropriate for estimating changes in CVD mortality of reduced lead exposure in adults? Is there an alternative conceptual model that would be preferred? Are there conditions when one model might be preferred over others?**

Conceptual model 4 seems the least applicable. The others each have strengths and weaknesses that are, for the most part, appropriately discussed. Probably also useful to note, as discussed elsewhere in the document, that the use of single blood lead no doubt entail measurement error, i.e., error in estimating the "true" measure of lead exposure that is biologically most relevant in terms of causing CV disease, both in terms of measurement error in the laboratory measurement itself; error in terms of not taking into account variations in blood lead over time; and error in terms of not reflecting what may be the most important metric biologically (cumulative exposure? Exposure at a certain period of life? Etc.). Overall, it could be argued (as Weisskopf has), that this error is basically non-differential misclassification of exposure, which, in turn, generally biases estimates of effect towards the null. In other words, each of the studies included in this document's analyses may be underestimating the true impact of lead exposure on CV mortality.

RESPONSE: Based on this and other reviewer comments, we will continue to include conceptual models 2 and 3 in the report and consider how best to implement these models in regulatory analysis. We will also revisit the text to consider expanding our discussion of measurement error and the resulting potential for attenuation bias.

c. **Does the applicability of the CRFs depend on the duration of the change in lead exposure expected to result from a policy change (e.g., short-term exposure reductions versus chronic exposure reductions)?**

In my opinion, cumulative lead exposure likely has a major if not dominant role in explaining the observed relationship between blood lead and CV mortality. Assuming this is true, the major impact of a policy change would not be felt for years.

RESPONSE: Based on this and other reviewers' comment, we will continue to include conceptual models 2 and 3 in the report and consider how best to implement these models in regulatory analysis.

7. Does the paper successfully identify and summarize important issues related to uncertainty and variability in the functions and their application? If not, how can it be improved?

a. **Are there critical uncertainties that have not been adequately considered?**

b. Given these uncertainties, does the approach proposed in the paper generate reasonable confidence in the estimates of the reduction in CVD mortality risk from reduced adult Pb exposure?

I've discussed this in various ways above. Overall, I think the document does quite a good job in the approach, analysis, interpretation, and conclusions, and I would support the notion that the paper generates "reasonable confidence" in the estimates provided. A final suggestion is that the report include a few paragraphs that summarize the background, approach and findings in lay language. I believe it is critical to be able to communicate to the general public what this analysis means for understanding the impacts of lead exposure, which still continues as one of the most widely prevalent environmental toxicant exposures in the world (including the US), on cardiovascular disease, which remains the number cause of death in the US, almost all developed countries, and, increasingly, developing countries throughout the world.

RESPONSE: We will revise the text to include a few summary paragraphs highlighting the background, approach, and findings for a non-technical audience.