Developing a Concentration-Response Function for Pb Exposure and Cardiovascular Disease-Related Mortality

June 2014

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1. Introduction

Lead (Pb) is a highly toxic pollutant that can damage neurological, cardiovascular, immunological, developmental, and other major organ systems (U.S. EPA, 2013). The neurological effects are particularly pronounced in children. Additionally, Pb exposure has been identified as one of the top 15 mortality risk factors (and top 10 cardiovascular risk factors) in the United States (U.S. Burden of Disease Collaborators, 2013). Typically, EPA Regulatory Impact Assessments for rules reducing Pb releases have focused on quantifying children's IQ as the primary category of monetized benefits, relying on an established methodology (U.S. EPA, 2008a). Benefits realized in the adult population are only discussed qualitatively. However, recent studies in the public health literature have found that a wide spectrum of adverse health outcomes can occur in people of all ages (U.S. EPA, 2013). In addition, a level of Pb exposure below which adverse effects do not occur has not been identified. This suggests that further declines in Pb exposure below today's levels could still yield important benefits in the adult population that are not currently being quantified in benefits estimates. Recent evidence has suggested that exposure to Pb in adults can result in cardiovascular disease (CVD) impacts; specifically, increases in hypertension, coronary heart disease, CVD, and cardiovascular disease-related mortality (CVD mortality) (National Toxicology Program, 2012; U.S. EPA, 2013).

A well-established quantitative approach to evaluating benefits due to reductions in Pb releases for adults does not exist. The objective of this project is to create a rigorous approach to quantify adult health benefits from a reduction in Pb exposure for CVD mortality, which would strengthen EPA's regulatory analyses and more completely characterize the effects of its programs. While we recognize the uncertainties and complexities in quantifying adult exposures to Pb, the process for estimating exposure is outside the scope of this report. The purpose of this report is to present a concentration-response function to estimate the number of cardiovascular disease deaths which would be avoided as a result of a decrease in Pb exposure.

In order to accomplish this objective, we reviewed the literature, identified key studies, and assessed them for their applicability to adult benefits estimation. We used the results from the most applicable study as the basis of a proposed concentration-response function for use in benefits estimation.

1.1 Available Literature

Two recent comprehensive government documents summarize the literature on the health impacts of Pb exposure: *EPA's Integrated Science Assessment for Lead* (U.S. EPA, 2013) (hereafter referred to as the EPA ISA or the EPA ISA report) and the *National Toxicology Program Monograph on Health Effects of Low-Level Lead* (National Toxicology Program, 2012) (hereafter referred to as the NTP Monograph). Given that these two documents already reviewed the literature through 2012 on adverse health effects associated with Pb exposure, we used them to identify studies that could serve as the basis of a function relating CVD to an adverse health outcome as a result of Pb exposure in the adult population.

1.1.1 EPA ISA

The EPA ISA report surveyed and evaluated policy-relevant science examining the relationship between Pb and human health. The report determined causality by an evaluation and synthesis of evidence from controlled human exposure, epidemiologic, and toxicological studies published since

the last review (this occurred in 2006). From the review of this literature and the conclusions reached in the previous review, the EPA ISA classified the relationship between Pb exposure and adverse health effects.

The EPA ISA causal determination categories are as follows:

- **Causal relationship:** Pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.
- **Likely to be a causal relationship:** Pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence, but potential issues remain.
- **Suggestive of a causal relationship:** Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited.
- **Inadequate to infer a causal relationship:** Available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
- **Not likely to be a causal relationship:** Evidence is suggestive of no causal relationship with relevant pollutant exposures.

The EPA ISA report determined there was a causal relationship between Pb exposure and health outcomes in the nervous, cardiovascular, renal, immune, and reproductive and developmental systems (U.S. EPA, 2013). The EPA ISA also determined a causal relationship between Pb exposure and effects on heme synthesis and red blood cell function. Lastly, they concluded there is a likely causal relationship between Pb exposure and cancer (U.S. EPA, 2013).

1.1.2 The NTP Monograph

The NTP Monograph summarizes the entire epidemiologic body of evidence for human health effects associated with low-level Pb exposure (less than 10 micrograms of Pb per deciliter of blood (<10 µg/dL)). This monograph does not focus on health effects at blood Pb levels >10 µg/dL because these effects are well established (National Toxicology Program, 2012). The NTP conducted a review of the epidemiological literature for low-level Pb association with the following health endpoints: cardiovascular, immunological, neurological, renal, and reproductive and developmental effects. From this evaluation, the NTP categorized its conclusions for these endpoints as follows:

- **Sufficient evidence of association:** Chance, bias, and confounding could be ruled out with reasonable confidence.
- **Limited evidence of association:** Chance, bias, and confounding could not be ruled out with reasonable confidence.
- **Inadequate evidence of association:** Available studies are insufficient in quality, consistency, or statistical power; or an association between exposure and health outcome is absent; or no data in humans are available.
- **Evidence of no association:** Several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood Pb levels <10 µg/dL)

are mutually consistent in not showing an association between exposure to the agent and any studied endpoint.

NTP found sufficient evidence of an association for select neurologic, cardiovascular, and reproductive endpoints in adults exposed with blood Pb levels < 10 µg/dL (National Toxicology Program, 2012).

1.2 Report Outline

We looked at the evidence presented in the EPA ISA (U.S. EPA, 2013), in conjunction with that in the NTP Monograph (National Toxicology Program, 2012), with the goal of choosing the most relevant endpoints for benefits estimation for regulations reducing Pb exposure in adults. Through this exercise, we selected CVD mortality as the best endpoint for developing a concentration-response function to inform a quantitative risk assessment–based approach to evaluating benefits due to reductions in Pb exposure. The remainder of this report explains our process for choosing CVD mortality as the selected endpoint (Section 2), the studies we considered as the potential basis for a concentration-response function (Section 3), and the derivation of the concentration-response function (Section 4). Additionally, in this report we explore the generalizability of the derived concentration-response function and present the benefits associated with a hypothetical example rule (Section 5) and propose a method by which to analyze the inherent uncertainty in the function (Section 6). Lastly, we discuss what additional steps could be taken to refine the Pb-CVD mortality function (Section 7).

2. Selection of Cardiovascular Disease-Related Mortality as the Health Endpoint

The EPA ISA and NTP Monograph reviewed the association between Pb exposure and adverse health impacts for more than 15 endpoints within six physiologic systems. This report focuses on the cardiovascular endpoint, and this section explains the process for selecting CVD mortality as the health endpoint of interest. In order to draw the conclusion that an exposure may result in an adverse health outcome, there must be a plausible mode of action by which the exposure can cause the health outcome. This is presented in Section 2.1. Sections 2.2 and 2.3 discuss the weight of evidence for cardiovascular morbidity and mortality, respectively.

2.1 Mode of Action for Pb and Cardiovascular Impacts

Pb is thought to impact the cardiovascular system in several ways. According to the EPA ISA, the mechanistic evidence from toxicological studies is strongest for the role of Pb-induced oxidative stress in hypertension (U.S. EPA, 2013). Multiple studies cited in the EPA ISA show that Pb changes enzymatic activity, leading to the increased formation and decreased breakdown of reactive oxygen species, which inactivate and sequester nitrogen dioxide, a vasodilator. The decrease in nitrogen dioxide, as a result of increased reactive oxygen species, results in constriction of blood vessels and therefore increased blood pressure. High blood pressure is a well-recognized risk factor for CVD and CVD mortality (Ezzati et al., 2006).

Another potential mechanism through which Pb exerts its cardiovascular toxicity is by altering the normal function of vascular cells, including endothelial and vascular smooth muscle cells (U.S. EPA, 2013). For example, Pb induces inflammatory damage to endothelial cells, which line the interior of blood vessels and help to regulate blood pressure (Cines et al., 1998; U.S. EPA, 2013). There is also evidence that Pb exposure stimulates vascular smooth muscle cell migration and proliferation. Each of these is a key event in the pathogenesis of atherosclerosis. Atherosclerosis is a key component of the pathological process of peripheral arterial disease, stroke, and coronary heart disease, all of which can cause CVD mortality (CDC, 2004).

Pb may also exert cardiovascular toxicity through disruption of calcium homeostasis. Evidence suggests that changes to calcium levels cause changes in heart rate variability, which have been associated with cardiovascular morbidity and mortality in older adults (U.S. EPA, 2013). Calcium-induced pro-coagulant activity may also lead to thrombosis, a risk factor for stroke and heart attack.

Hypertension and atherosclerosis have been linked to additional Pb-induced modes of action, including hormonal system dysfunction, sympathetic nervous system activation, renal system dysfunction, and vasomodulator imbalance. For more information on Pb's mode of action, the reader is referred to pages 4-324 through 4-404 of EPA's ISA report.

2.2 EPA ISA and NTP Monograph Cardiovascular Morbidity Findings

Many endpoints fall under the category of cardiovascular morbidity. The EPA ISA report specifically examined and made explicit conclusions on the association between Pb exposure and increased blood pressure or the resulting clinical outcome of hypertension, subclinical atherosclerosis, coronary heart

disease, and cerebrovascular disease. The NTP monograph examined and made explicit conclusions on blood pressure or the resulting clinical outcome of hypertension, heart rate variability, electrocardiogram abnormalities, clinical CVD (in general and by specific endpoint), and CVD mortality.

Given that the purpose of this report is to identify an association between Pb exposure and monetary benefits from reduced exposure, we concentrate on summarizing the evidence for only those endpoints that are readily quantifiable and monetizable. Therefore, in this section we summarize the evidence for increased blood pressure or the resulting clinical outcome of hypertension, clinical CVD, and cerebrovascular disease. The weight of evidence for these endpoints was examined by both the EPA ISA and the NTP monograph. The NTP and EPA ISA conclusions are summarized in Exhibit 1.

Exhibit 1. Conclusions from the EPA ISA and NTP Monograph on Readily Quantifiable Cardiovascular Morbidity Effects Experienced in Adults Associated with Pb Exposure

Effect	Definition	EPA ISA Conclusion	NTP Conclusion
Blood pressure	The force exerted by the heart against the walls of the arteries (measured in millimeters of mercury (mmHG)), with a maximum during the pumping phase of the heartbeat (systolic blood pressure, SBP) and a minimum when the heart muscle relaxes between beats (diastolic blood pressure, DBP).	*Causal:* Prospective epidemiologic studies adjusting for potential confounders consistently find associations. Supported by cross-sectional studies, meta-analyses, animal studies and plausible modes of action. Uncertainties remain regarding the timing, frequency, duration, and level of Pb exposures contributing to the effects observed in epidemiologic studies (p. lxxiv).	*Sufficient* evidence that blood Pb levels <10 µg/dL are associated with increases in blood pressure (BP) and hypertension. The association between higher Pb levels and higher BP is most consistent in studies of bone Pb (p. 80).
Hypertension	Medical term for high blood pressure (currently, SBP ≥140 or DBP ≥90) compared to an optimal BP of <120/80 mmHg. BPs of 120-139/80-89 mmHg are considered prehypertension.		

Effect		Definition	EPA ISA Conclusion	NTP Conclusion
Cardiovascular Disease	Coronary heart disease	Narrowing of the arteries that supply blood and oxygen to the heart muscle, caused by atherosclerosis, which can result in a myocardial infarction (also called ischemic heart disease (IHD)).	*Causal*: Prospective studies consistently find associations of Pb biomarkers with cardiovascular disease -related mortality and morbidity, specifically myocardial infarction (MI), IHD, or heart rate variability. This is supported by animal studies. Uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies (p. lxxxv).	Clinical CVD (general): *Limited* evidence that blood Pb levels <5 µg/dL are associated with clinical CVD (p. 97). Clinical CVD (specific): *Inadequate* evidence to evaluate a potential association between Pb exposure and specific CVDs (p. 97).
	Peripheral artery disease (for EPA included in the category of subclinical atherosclerosis (U.S. EPA, 2013, p. 1-27)	Narrowing of arteries carrying blood to the arms and legs, caused by atherosclerosis.	*Suggestive of a causal relationship:* (categorized as subclinical atherosclerosis by EPA). Cross-sectional analyses of National Health and Nutrition Examination Survey (NHANES) data find associations. Animal studies are limited to mode-of-action studies, which demonstrate how Pb may initiate atherosclerotic vessel disease.	
	Cerebrovascular Disease	Disease of the blood vessels which supply the brain. Often caused by atherosclerosis and can lead to stroke.	*Inadequate to infer a causal relationship:* Available data are of insufficient quantity, quality, and/or consistency, but modes of action are demonstrated (p. lxxxv).	*Limited* evidence: There are few replicated studies (p. 76).

Sources: American Heart Association (2011); MedicineNet.com (2012); National Toxicology Program (2012); U.S. EPA (2013)

2.3 EPA ISA and NTP Monograph Cardiovascular Disease-Related Mortality Findings

In addition to examining the impacts from cardiovascular morbidity, CVD mortality was also examined by the EPA ISA (under the category of coronary heart disease) and the NTP Monograph. A summary of the findings on the conclusions from the EPA ISA and NTP Monograph for CVD mortality are summarized in Exhibit 2. Detailed summaries of all the studies considered can be found in Section 3 and Appendix A of this document.

Exhibit 2. Conclusions from the EPA ISA and NTP Monograph on Cardiovascular Disease-Related Mortality in Adults Associated with Pb Exposure

Effect	Definition	EPA ISA Conclusion	NTP Conclusion
Cardiovascular disease-related mortality (for EPA included under the category for coronary heart disease)	Death attributed to heart or circulatory causes	Included in *causal* determination for coronary heart disease (see Exhibit 1). Despite the differences in design and methods across studies, with few exceptions associations between higher levels of Pb biomarkers and higher risk of [coronary heart disease]-related mortality were consistently observed (p. 4-412).	*Limited* evidence that blood Pb levels <10 µg/dL are associated with increased mortality from cardiovascular causes (p. 90)

Sources: (American Heart Association, 2011; National Toxicology Program, 2012; U.S. EPA, 2013)

The EPA ISA deemed the association between Pb exposure and coronary heart disease (including cardiovascular-related mortality) to be *causal*. Specifically, EPA stated, "despite the differences in design and methods across studies, with few exceptions associations between higher levels of Pb biomarkers and higher risk of [coronary heart disease]-related mortality were consistently observed" (p. 4-412, U.S. EPA, 2013).

On the other hand, the NTP Monograph concluded that there is "*limited* evidence that blood Pb levels <10 µg/dL are associated with increased mortality from cardiovascular causes" and that the "association between increased CVD mortality and increased blood Pb was supported by three prospective studies but not supported by two prospective studies, one of which reported a significant association with bone Pb" (National Toxicology Program, 2012, p. 90).

The two prospective studies NTP is referring to that do not support the association between blood Pb increases and CVD mortality are Møller and Kristensen (1992) and Weisskopf et al. (2009). However, Møller and Kristensen (1992) examined the risk of developing coronary heart disease and cardiovascular disease using both fatal and nonfatal cases. They did not examine the risk of CVD mortality without the non-fatal cases included in the analysis. Weisskopf et al. (2009) found no

association between blood Pb and cardiovascular-related mortality but did find an association when bone Pb was used as the marker of exposure (more detail on this study can be found in Section 3.4). The findings should be considered alongside the fact that the method of selection for the Normative Aging Study (NAS) cohort used in the Weisskopf study suffers from selection bias. The NAS cohort used in the Weisskopf et al. (2009) study is weighted toward individuals without CVD, given that in order to be entered into the cohort you could not have prior CVD. For older individuals this creates a strong selection bias toward heart-healthy people (Weisskopf, 2013). Therefore, the null results may be a product of this selection bias. The details about the Weisskopf study are outlined in more detail in Section 3.4. Regardless, personal communication with Dr. Weisskopf revealed that there were errors in the analysis, a correction is to be published in *Circulation,* and the currently published results should not be used. Once the corrected results are published, we will reexamine the study.

As described in Section 2.1, both the EPA ISA and NTP Monograph gave the strongest weight-of-evidence designation to increases in blood pressure. However, EPA also determined a "causal" weight of evidence for coronary heart disease, and included CVD mortality in this category. Although NTP determined the association between Pb and CVD mortality to be "limited" (its second highest category under "sufficient"), this determination was based on the fact that two studies did not support the association. However, as stated in the previous paragraph, at least one of the two studies that do not support the association has issues which are being corrected by the authors. Therefore, given that CVD mortality is more useful from a benefits analysis perspective and there is ample weight of evidence to support the association, we chose this endpoint for the development of a concentration-response function. The next section evaluates the literature selected by the EPA ISA (U.S. EPA, 2013) and the NTP Monograph (National Toxicology Program, 2012) to determine the best evidence from which to develop a concentration-response function explaining the relationship between Pb exposure and CVD mortality.

3. Assessment of Literature

To estimate a concentration-response function between blood Pb and CVD mortality, it is necessary to identify one or more suitable studies as the basis of the function. To be useful for benefits analyses, a study should be applicable to the general population and use sound scientific methods in the approach. We reviewed each of the eight studies considered by the EPA ISA and the NTP Monograph to see if their results could be extrapolated to the general population. For this initial screening, we considered the following criteria:

- The study sample is representative of the adult general population or a large sector of the general adult population (e.g., men/women over the age of 40). Studies of patients with a particular disease, for example, do not represent a major portion of the population and would not be very useful for estimating the primary concentration-response function for a benefits analysis applicable to the general population.
- The study reports average blood Pb levels <10 µg/dL. These levels are more representative of the current blood Pb levels in the United States, and consistent with the criteria for inclusion used by NTP.
- The study used established methods and was included in the NTP or EPA weight-of-evidence determinations.

Exhibit 3 displays the eight studies identified by the NTP Monograph and the EPA ISA report that examined the association between blood Pb and CVD mortality. Only one study, Weisskopf et al. (2009), also considered bone Pb as a biomarker. There were no studies identified that looked only at bone Pb and CVD mortality.

As summarized in Exhibit 3, Menke et al. (2006), Schober et al. (2006), Khalil et al. (2009), and Weisskopf et al. (2009) all have populations in their study that would allow their results to be generalizable to all or significant portions of the U.S. adult population for a national benefits analysis.[1] We closely examined these four studies to determine if they would be useful in creating a concentration-response function for blood Pb level and risk of CVD mortality. This included evaluating the statistical significance of their findings. Summaries of the other five[2] studies can be found in Appendix B of this document.

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[1] The Weisskopf et al. (2009) cohort excluded people with prior CVD. If these findings are considered in the future, it should be noted that 3.6% of the population between the ages of 18 and 44 and 12.8% of the population between the ages of 45 and 64 have cardiovascular disease (CDC, 2012b). Additionally, consideration will need to be given to applying the results to older individuals, over 65 years of age, given that at least 25% of the older population has cardiovascular disease (CDC, 2012b).

[2] Given that Møller and Kristensen's 1992 study did not examine blood Pb as it relates specifically to cardiovascular disease-related mortality, we will not further consider it in the development of the concentration-response function. It is included in Appendix B since it was considered in the NTP Monograph.

Exhibit 3. Summary of Population Characteristics for Studies Examining the Association between Blood Pb Levels and Cardiovascular Disease-Related Mortality

Study	Population Representative of a Significant Portion of the Adult Population	Reported Average Blood Pb Levels <10 µg/dL (Mean Blood Pb Level unless Otherwise Noted)
Cocco et al. (2007) *Causes of death among lead smelters in relation to the glucose-6-phosphate dehydrogenase polymorphism*		[a]
Khalil et al. (2009) *Association of blood lead concentrations with mortality in older women: a prospective cohort study*	X	X (5.3 µg/dL)
Lin et al. (2011) *Association of blood lead levels with mortality in patients on maintenance hemodialysis*		(median: 10.4 µg/dL)
Lustberg & Silbergeld (2002) *Blood lead levels and mortality*	X	(14.0 µg/dL)
Menke et al. (2006) *Blood lead below 0.48 µmol/l (10 µg/dL) and mortality among US adults*	X	X (2.58 µg/dL)
Neuberger et al. (2009) *Potential health impacts of heavy-metal exposure at the Tar Creek Superfund site, Ottawa County, Oklahoma*	X	[a]
Schober et al. (2006) *Blood lead levels and death from all causes, CVD, and cancer: results from the NHANES III mortality study*	X	X (median: 4.14 µg/dL)[b]
Weisskopf et al. (2009) *A prospective study of bone lead concentration and death from all causes, CVD, and cancer in the Department of Veterans Affairs Normative Aging Study*	X	X (5.6 µg/dL)

[a] No blood Pb data presented for this study.

[b] No overall mean or median blood Pb level was presented in Schober et al. (2006). This value is a calculated weighted median blood Pb level based on the cohort population characteristics presented in Table 1 of Schober et al. (2006).

In our evaluation of Menke et al. (2006), Schober et al. (2006), Khalil et al. (2009), and Weisskopf et al. (2009), we determined there are two categories into which the studies may fall:

- The study presents a continuous concentration-response function or presents a result (e.g., a relative risk associated with a given change in blood Pb levels) based on an underlying continuous concentration-response function for blood Pb and CVD mortality risk. This type of study is the most useful.
- The study presents categorical comparisons of risk of CVD mortality associated with different categories of blood Pb level based on a categorical analysis. If applicable, we contacted the authors to see if the underlying data are available to estimate a continuous concentration-response function. Since using categorical data to estimate the continuous function requires additional assumptions and modeling, we gave preference to studies that provide continuous data.

As discussed above, Schober et al. (2006), Menke et al. (2006), Khalil et al. (2009), and Weisskopf et al. (2009) have results that can be extrapolated to a large portion of the population for a national benefits analysis. In some cases, we contacted study authors for details and/or data not available in the publication. A more detailed overview of the methods and results of each of these four studies is presented in the subsequent subsections.

3.1 Detailed Summary of Schober et al. (2006)

Schober et al.'s (2006) *Blood Lead Levels and Death from All Causes, Cardiovascular Disease, and Cancer: Results from the NHANES III Mortality Study* examined the association between blood Pb levels and all-cause and cause-specific mortality of 9,686 participants in NHANES III who were 40 years of age or older. The mean blood Pb level for the population was not presented, but approximately 94% of the study participants had blood Pb levels less than 10 µg/dL. We calculated the median blood Pb level to be approximately 4.14 µg/dL based on the median blood Pb levels and sample sizes presented in Table 1 of Schober. The median length of follow-up was 8.55 years, during which there were 2,515 deaths. Using the International Classification of Disease (Tenth Revision), Schober et al. identified death due to malignant neoplasms (ICD-10 codes C00-C97) and major CVD (ICD-10 codes I00-I78).

Schober et al. categorized blood Pb into three categories: <5 µg/dL, 5 to <10 µg/dL, and ≥10 µg/dL. The authors used Cox proportional hazard regression analysis, with age[3] as the time scale, to examine the hazard of mortality from all causes, cancer, and CVD using the categories outlined in the previous paragraph. The baseline hazard was stratified by age, using 6-year intervals, controlling for potential cohort difference in cumulative exposure to Pb before the late 1970s. Additionally, because current Pb exposure (and subsequently blood Pb levels) continued to decline over the 6-year period of blood collection, the authors also stratified based on survey phase. Multivariate proportional hazard models were used to examine the association between blood Pb and mortality, while adjusting for potential confounders. Additionally, all two-way interactions with blood Pb category were assessed. Further, Schober et al. stated that because the cancer mortality and blood Pb relationship was different for men

[3] Age was defined as a participant's age at the baseline examination.

and women in a previous study of the NHANES II cohort, they also stratified multivariate models separately for males and females, and sex was included in their final model as a confounder.

Schober et al. assessed the concentration-response relationship of blood Pb and mortality in two ways. First, the multivariate adjusted relative risks for the three blood Pb categories were tested for trend. The median values for each Pb group were placed in a linear term and analyzed using a Wald test. Second, using a five-knot cubic regression spline, they evaluated the log-transformed[4] blood Pb concentrations as a continuous variable, and used a Wald test to evaluate the concentration-response relationship.

The number of deaths and multivariate-adjusted relative risks of mortality due to all causes, CVD, and cancer are presented in Exhibit 4. There were a total of 2,485 deaths from all causes, 1,189 from CVD, and 543 from cancer. All multivariate models were adjusted for sex, race/ethnicity, education level, and smoking status. None of the interaction terms had large effects on the model, nor did they alter the direction of the Pb-mortality relationship, and therefore they were not included in the final models. For mortality due to all causes and CVD, there was a pattern of increasing risk with increasing blood Pb. For all-cause, cardiovascular, and cancer deaths for all age groups, the trend tests exploring a concentration-response relationship were significant. The results of this analysis are presented in Exhibit 4.

[4] Because of the skewed distribution of blood Pb levels, the authors log-transformed the blood Pb measurements.

Exhibit 4. Multivariable Adjusted Relative Risks for All-Cause, Cancer, and Cardiovascular Disease-Related Mortality by Blood Level and Age Category (Schober et al., 2006)

Cause of Death/ Blood Pb Level	Number of Deaths	Relative Risk (95% CI) by Age Category (Years)			
		40-74	75-84	>85	All
All causes					
<5 µg/dL	1,402	1	1	1	1
<5-9 µg/dL	828	1.30 (1.03-1.65)	1.38 (1.04-1.83)	0.98 (0.85-1.14)	1.24 (1.05-1.48)
≥10 µg/dL	255	1.73*** (1.28-2.35)	1.39** (0.93-2.08)	1.67 (1.11-2.53)	1.59*** (1.28-1.98)
Cardiovascular disease					
<5 µg/dL	684	1	1	1	1
<5-9 µg/dL	394	1.11 (0.79-1.56)	1.41 (0.87-2.28)	1.07 (0.87-1.31)	1.20 (0.93-1.55)
≥10 µg/dL	111	1.47 (0.93-2.33)	1.71** (0.94-3.09)	1.45 (0.85-2.48)	1.55* (1.16-2.07)
Cancer					
<5 µg/dL	282	1	1	1	1
<5-9 µg/dL	194	1.44 (0.91-2.28)	1.46 (1.03-2.07)	1.44 (0.92-2.26)	1.44 (1.12-1.86)
≥10 µg/dL	67	2.27* (1.38-3.74)	0.80 (0.38-1.69)	2.2* (1.13-4.29)	1.69* (1.14-2.52)

Note: Variables adjusted for sex, race/ethnicity, education, and smoking status.
*p-value for trend test <0.01
**p-value for trend test <0.05
***p-value for trend test <0.001
Source: Schober et al. (2006, Table 2).

The work by Schober et al. (2006) provides supporting evidence that blood Pb is associated with all-cause and CVD mortality. We contacted the study authors to determine if a concentration-response function was available for the relationship between CVD mortality and blood Pb. Although Dr. Schober and her co-author, Dr. Mirel, were willing to help, it turned out not to be feasible to retrieve actual functions. Therefore, if this study were used, a concentration-response function would need to be estimated from Schober's categorical analysis.

3.2 Detailed Summary of Menke et al. (2006)

Similar to Schober et al. (2006), Menke et al. (2006) also used NHANES III data to examine the association between blood Pb levels and all-cause and cause-specific mortality among U.S. adults who have blood Pb levels below 10 µg/dL in their study, *Blood Lead Below 0.48 µmol/L (10 µg/dL) and Mortality Among US Adults.* However, Menke et al. (2006) included 13,946 participants 20 years of age and older. Additionally, mortality follow-up was approximately 12 years, and Menke et al. (2006) included additional ICD-9 codes when examining the cause of death. The mean blood Pb level for the participants in the Menke et al. (2006) study was 2.58 µg/dL.

Menke et al. (2006) performed several statistical analyses. In one statistical analysis, Menke et al. categorized the participants into blood Pb tertiles based on the weighted population distribution. The tertiles were <1.93 µg/dL, 1.94 µg/dL – 3.62 µg/dL, ≥3.63 µg/dL. To analyze the association between blood Pb and mortality, follow-up for each participant was calculated as the time between their NHANES III examination and the date of death, the date on which they turned 90 years of age, or December 31, 2000. The HRs and 95% CIs were calculated by multivariable Cox regression models for all-cause cardiovascular, myocardial infarction, stroke, and cancer mortality by comparing each tertile with the first (low Pb) tertile. When comparing the second (middle) tertile to the first tertile an increase was seen, but this was not statistically significant. When comparing the third tertile to the first tertile, a statistically significant increase in risk was found (see Exhibit 5). As shown in Exhibit 5, the study authors performed three analyses to adjust for various potential confounders, and CVD mortality remained statistically significantly associated with blood Pb levels in all three models. Cancer mortality was not found to be associated with Pb exposure.

Exhibit 5. Hazard Ratios and 95% Confidence Intervals of All-Cause, Cardiovascular Disease, Myocardial Infarction, and Stroke Mortality Associated with Tertile of Pb (Menke et al., 2006)

	Tertile 1 (<0.09 µmol/L or <1.93 µg/dL)	Tertile 2 (0.09-0.17 µmol/L or 1.94-3.62 µg/dL)	Tertile 3 (≥0.18 µmol/L or ≥3.63 µg/dL)	P_{trend}
All-cause mortality, n	252	470	939	
Age, race-ethnicity, and sex adjusted	1.00	0.97 (0.76–1.23)	1.37 (1.15–1.64)	<0.001
Multivariable 1 adjusted*	1.00	0.93 (0.73–1.19)	1.30 (1.08–1.56)	<0.001
Multivariable 2 adjusted†	1.00	0.91 (0.72–1.15)	1.25 (1.04–1.51)	0.002
Cardiovascular disease mortality, n	104	219	443	
Age, race-ethnicity, and sex adjusted	1.00	1.01 (0.68–1.51)	1.51 (1.07–2.14)	0.004
Multivariable 1 adjusted*	1.00	1.06 (0.70–1.60)	1.64 (1.14–2.35)	0.001
Multivariable 2 adjusted†	1.00	1.03 (0.69–1.55)	1.55 (1.08–2.24)	0.003
Myocardial infarction mortality, n	50	83	234	
Age, race-ethnicity, and sex adjusted	1.00	0.99 (0.55–1.79)	1.70 (0.99–2.90)	0.011
Multivariable 1 adjusted*	1.00	1.05 (0.56–1.97)	2.01 (1.12–3.61)	0.003
Multivariable 2 adjusted†	1.00	1.02 (0.55–1.89)	1.89 (1.04–3.43)	0.007

* Adjustment included age, race-ethnicity, sex, diabetes mellitus, body mass index (BMI), current or former smoking, alcohol consumption, physical activity, low income, c-reactive protein (CRP), total cholesterol, high school education, urban residence, and post-menopausal status.
† Adjustment includes variables in model 1, hypertension, and level of kidney function.
Sample sizes (n) refer to the number of events.
Source: Menke et al. (2006, Table 2).

Tests for linear trend across tertiles of blood Pb were computed by including tertile of Pb as continuous variable in the Cox regression models. The trend analysis found statistically significant increases in mortality risk for all causes of mortality analyzed except cancer. The results of this analysis are also presented in Exhibit 5 and support the finding of a concentration-response relationship between blood Pb and CVD mortality.

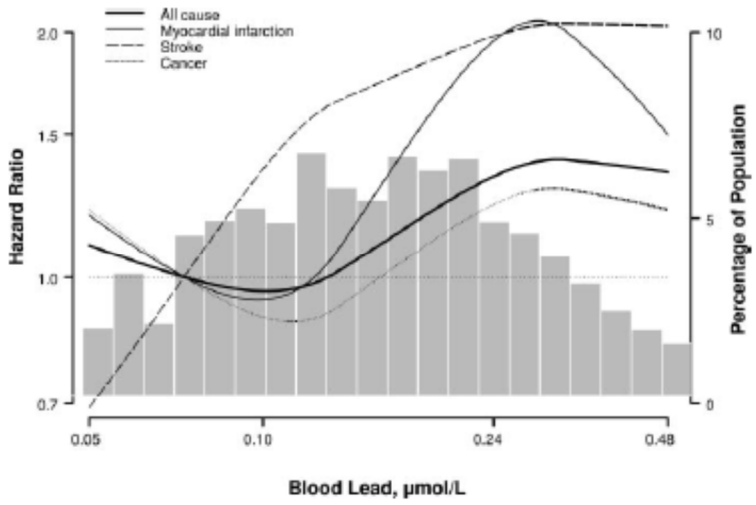
Menke et al. (2006) also explored the concentration-response relationship of blood Pb level with all-cause, myocardial infarction, and stroke mortality using a restricted quadratic spline with knots at the

10th, 50th, and 90th percentiles of blood Pb distribution (Exhibit 6). This analysis revealed that the increase in all-cause and myocardial infarction occurred at blood Pb levels > 2.0 µg/dL (0.10 µmol/L). Stroke increased monotonically at all blood Pb levels included in the spline analysis (1 to 10 µg/dL). Quadratic spline results were not presented for CVD.

In a third analysis, due to the skewness of the distribution of blood Pb, Pb was log-transformed and treated as a continuous variable. The study authors calculated HRs for a 3.4 increase in blood Pb levels or the difference between the logged 80th (4.92 µg/dL) and 20th (1.46 µg/dL) percentiles of blood Pb distribution. After the multivariate adjustment,[5] the HR for a 3.4-fold increase in blood Pb level was 1.34 (95% CI = 1.16 to1.54) for all-cause mortality, 1.53 (1.21-1.94) for CVD mortality, 1.78 (1.18 to 2.67) for myocardial infarction, and 1.59 (1.08-2.34) for stroke mortality. The results from the all-cause and CVD mortality analyses are presented in Exhibit 7.

Menke et al. (2006) also determined the association between blood Pb as a continuous variable and mortality for subgroups defined by age, race-ethnicity, sex, menopausal status, urban or rural residence, cigarette smoking, overweight, diabetes mellitus, hypertension, and level of estimated glomerular filtration rate (GFR). However, no subgroup interaction terms were statistically significant at the 5% level. Their findings are summarized in Exhibit 7.

Exhibit 6 Multivariate Adjusted Relative Hazard of Mortality Associated with Blood Lead Levels between 0.05 µmol/L (1 µg/dL) and 0.48 µmol/L (10 µg/dL)



Source: Menke et al. (2006, Figure 1). Note: Histogram of blood lead levels is superimposed in the background and displayed on the right axis.

[5] Adjustment included age, race-ethnicity, sex, diabetes mellitus, BMI, current or former smoking, alcohol consumption, physical activity, low income, c-reactive protein (CRP), total cholesterol, high school education, urban residence, and post-menopausal status, hypertension, and level of kidney function (Personal Communication with Andy Menke, 2013).

Exhibit 7. Multivariate Adjusted Relative Hazards[1] of All-Cause and Cardiovascular Disease-Related Mortality

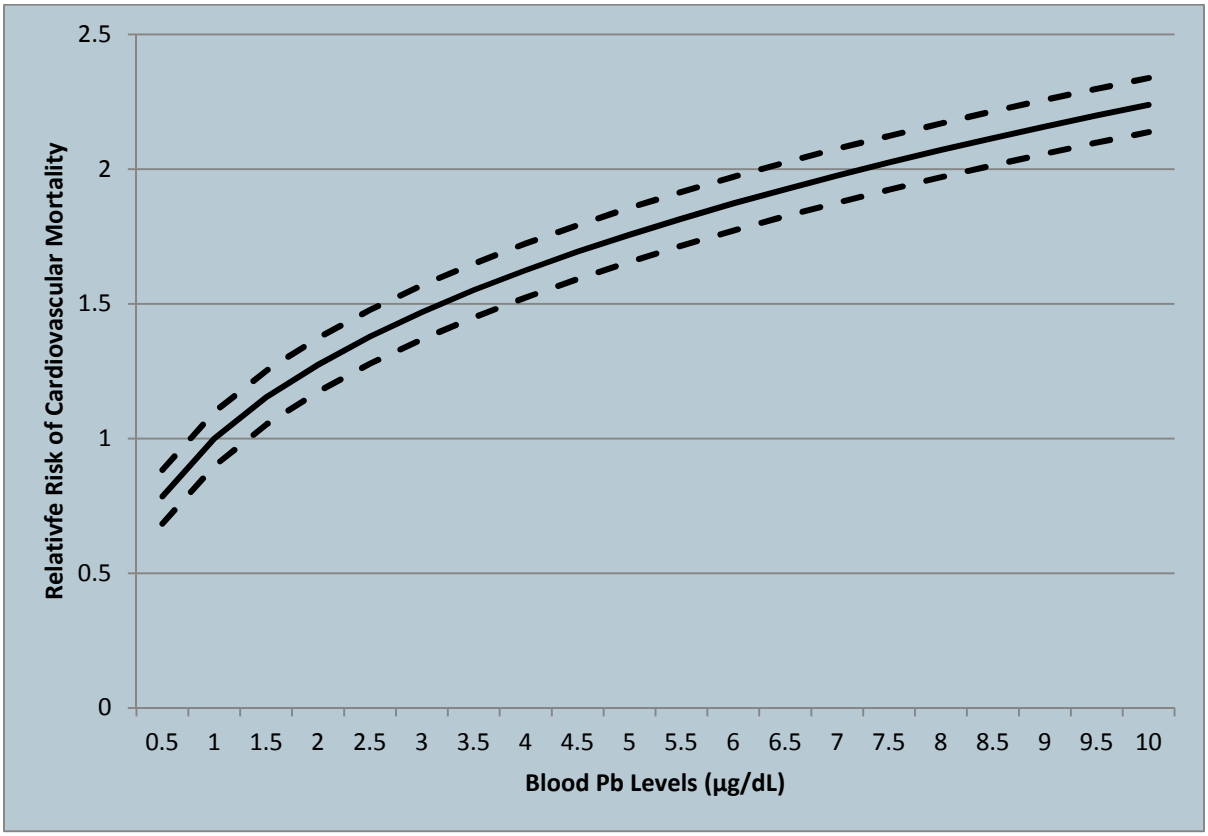
Subgroup	HR of All-Cause Mortality (95% CI)	HR of Cardiovascular Disease-Related Mortality (95% CI)
Age (years)		
<60	1.75 (1.25-2.44)	2.00 (1.24-3.22)
≥60	1.31 (1.08-1.58)	1.49 (1.12-1.99)
Race-ethnicity		
Non-Hispanic white	1.32 (1.09-1.60)	1.49 (1.12-1.99)
Non-Hispanic black	1.23 (0.99-1.52)	1.13 (0.79-1.61)
Mexican-American	1.17 (0.86-1.60)	1.55 (0.90-2.68)
Sex and menopausal status		
Male	1.41 (1.11-1.78)	1.35 (0.84-2.18)
Female	1.24 (1.00-1.54)	1.63 (1.25-2.11)
Pre-menopausal	1.02 (0.54-1.95)	2.71 (0.93-7.91)
Post-menopausal	1.24 (1.00-1.54)	1.46 (1.04-2.03)
Residence		
Rural	1.28 (1.05-1.54)	1.41 (1.01-1.96)
Urban	1.42 (1.18-1.72)	1.75 (1.19-2.56)
Smoking		
Never	1.21 (0.93-1.58)	1.57 (1.10-2.24)
Former	1.61 (1.33-1.94)	2.07 (1.49-2.89)
Current	1.34 (0.96-1.87)	1.05 (0.54-2.04)
Body mass index (kg/m^2)		
<25	1.51 (1.16-1.96)	2.02 (1.32-3.11)
≥25	1.28 (1.03-1.58)	1.34 (0.94-1.91)
Hypertension		
No	1.31 (1.08-1.58)	1.48 (0.96-2.26)
Yes	1.32 (1.09-1.60)	1.49 (1.15-1.94)
Diabetes		
No	1.37 (1.19-1.58)	1.59 (1.31-1.92)
Yes	1.12 (0.73-1.71)	1.16 (0.67-2.00)
Estimated glomerular filtration rate (ml/min/1.73m^2)		
<60	1.44 (1.01-2.06)	1.75 (1.06-2.88)
≥60	1.32 (1.12-1.56)	1.49 (1.18-1.89)
Overall	**1.34 (1.16-1.54)**	**1.53 (1.21-1.94)**

[1]Hazard ratios were calculated for a 3.4-fold increase in blood Pb with log–blood Pb as a continuous variable. This increase corresponds to the difference between the 80th and 20th percentiles of the blood Pb distribution (4.92 µg/dL versus 1.46 µg/dL, respectively).

Source: Menke et al. (2006, Figure 2).

The results presented in Exhibit 7 are based on a continuous function that can be used as the basis of the concentration-response function for a benefits analysis. For each 3.4-fold increase in blood Pb level, there is a subsequent 53% increase in risk of CVD mortality for the adult population. This function is represented by the plot in Exhibit 8, which we generated based on the overall HR.

Exhibit 8. Illustrative Example of the Function from Menke et al. (2006) Representing the Risk of CVD Mortality as a Result of a Change in Blood Pb Relative to a Reference Level of 1 µg/dL



Menke et al.'s (2006) study results meet the criteria of having a generalizable concentration-response function that can be used, along with other data, to estimate benefits for adults who would have a reduction in Pb exposure as the result of a hypothetical regulation. Additionally, this study uses the same NHANES cohort as the Schober et al. (2006) paper but includes a wider age range of individuals, making their results more applicable to the adult general population. It is important to note that in addition to examining the relationship between blood Pb and CVD mortality, Menke et al. (2006) also found a statistically significant relationship between blood Pb and all-cause mortality, myocardial infarction mortality, and stroke mortality. CVD mortality was selected as the endpoint of preference because there was strong weight of evidence in the literature and it proved most useful for a benefits analysis compared to other endpoints (see Section 2).

The details of developing a concentration-response function with the data presented in Menke et al. (2006) are presented in Section 4.

3.3 Detailed Summary of Khalil et al. (2009)

Khalil et al.'s (2009) *Association of Blood Lead Concentrations with Mortality in Older Women: A Prospective Cohort Study* used the ancillary Pb study of the Study of Osteoporotic Fractures, a

longitudinal cohort study that enrolled white women aged 65–87 at either the University of Pittsburgh or University of Maryland clinics, to evaluate the blood Pb levels of 533 women aged 65–87 in association with all-cause and cause-specific mortality. The population's mean blood Pb concentration was 5.3 ± 2.3 µg/dL. The study authors categorized the participants into three groups depending on their blood Pb levels. The groups were ≤3 µg/dL (lower 15th percentile), 4-7 µg/dL, and ≥8 µg/dL (upper 15th percentile). This categorization was determined a priori based on a previous study of blood Pb and cognitive function; however, initial analysis suggested that mortality was only significant at the highest 15th percentile and that only the top quintile (80th percentile) showed elevated risk of death; therefore, the study authors combined categories to create only two categories, <8 µg/dL and ≥8 µg/dL. This varies from the Menke et al. (2006) findings in post-menopausal women. It is worth noting that this study has a substantially smaller sample size than Menke et al. (2006).

Deaths were confirmed by death certificate. The authors recorded the underlying cause of death using ICD-9-CM codes for CVD including all diseases of the circulatory system except those involving veins and lymphatics [ICD-9-CM codes 425, 429.2, 440–444, 428, 401–404, 410–414, 430–438, and 798]; coronary heart disease (CHD) [ICD-9-CM codes 410–414]; stroke [ICD-9-CM codes 430–438]; cancer [ICD-9-CM codes 140–239]; and all other deaths.

Using Cox proportional hazards regression analysis, Khalil et al. (2009) estimated the HRs and 95% CIs of death in the high Pb group (≥8 µg/dL) compared to the low Pb group (<8 µg/dL) using a multivariable model. Their findings are summarized in Exhibit 9.

Exhibit 9. Hazard Ratios and 95% Confidence Intervals of All-Cause Mortality by Blood Pb Concentrations

Cause of Death	Deaths	Blood Pb Concentration (µg/dL) [µmol/L]		P_{value}
		(< 8) [< 0.384]	(≥ 8) [≥ 0.384]	
All cause death, n (Col %)	123	96 (21%)	27 (34%)	0.018*
Age, clinic adjusted		1.0	1.73 (1.12, 2.68)	0.014
Multivariate adjusted [a]		1.0	1.59 (1.02, 2.49)	0.041
Cardiovascular disease [b], n(%)	54	41 (9)	13 (16)	0.044*
Age, clinic adjusted		1.0	1.90 (1.00, 3.63)	0.054
Multivariate adjusted [a]		1.0	1.78 (0.92, 3.45)	0.089
Coronary heart disease [c], n(%)	23	15 (4)	8 (11)	0.006*
Age, clinic adjusted		1.0	3.54 (1.48, 8.45)	0.004
Multivariate adjusted [a]		1.0	3.08 (1.23, 7.70)	0.016
Stroke [d], n(%)	21	17 (4)	4 (5)	0.578*
Age, clinic adjusted		1.0	1.16 (0.34, 4.00)	0.816
Multivariate adjusted [a]		1.0	1.13 (0.34, 3.81)	0.840
Cancer [e], n(%)	38	30 (7)	8 (10)	0.262*
Age, clinic adjusted		1.0	1.70 (0.77, 3.75)	0.185
Multivariate adjusted [a]		1.0	1.64 (0.73, 3.71)	0.231
All other deaths [f], n(%)	31	25 (7)	6 (10)	0.289*
Age, clinic adjusted		1.0	1.51 (0.61, 3.72)	0.370
Multivariate adjusted [a]		1.0	1.22 (0.48, 3.10)	0.673

*Chi-square p-value only for percentage of deaths in two blood Pb strata; the rest are hazard ratio p-values.

[a] The multivariate model included the following: age, clinic, BMI, education, smoking, alcohol intake, estrogen use, hypertension, walking for exercise, diabetes, and total hip bone mass density.

[b] ICD9 Code: All deaths due to CVD, including all diseases of circulatory system except those involving veins and lymphatics: 425, 429.2, 440–444, 428, 401–404, 410–414, 430–438, and 798.

[c] ICD9 Code: Deaths due to coronary heart disease: 410–414.

[d] ICD9 Code: Deaths due to stroke: 430–438.

[e] ICD9 Code: Deaths due to cancer: 140–239.

[f] ICD9 Code: All other deaths: Non CVD and noncancer deaths.

Source: Khalil et al. (2009, Table 5).

Although the Khalil et al. (2009) results support the association between Pb exposure and cardiovascular-related mortality to a portion of the adult U.S. population, we will not use the study to develop a concentration-response function because the results are less applicable to the entire adult U.S. population due to the focus on older women and the high average blood Pb levels among participants. Additionally, there is no underlying continuous concentration-response function reported.

3.4 Detailed Summary of Weisskopf et al. (2009)

Weisskopf et al.'s (2009) *A Prospective Study of Bone Lead Concentration and Death from All Causes, Cardiovascular Diseases, and Cancer in the Department of Veterans Affairs Normative Aging Study* examined the association of both blood and bone Pb levels and mortality. The authors measured bone Pb levels in the tibia (n = 863), patella (n = 860), and blood Pb (n = 1,235) in participants in the Department of Veterans Affairs Normative Aging Study, a cohort of community-dwelling elderly men from the greater Boston area. The average patella and tibia bone Pb concentrations were 31.2 (SD = 19.4) and 21.8 (SD = 13.6) µg/g bone mineral, respectively. The average blood Pb concentration measured at baseline was 5.6 (SD = 3.4) µg/dL, and the geometric mean was 4.8 µg/dL. To ascertain death, the study authors sent birthday cards and supplemental questionnaires to study participants. Next of kin or postal authorities notified the study authors if an individual had passed. Additionally, vital records of the Veterans Affairs and the Social Security Administration Death Master File were used to pick up possible unreported death, allowing for nearly 100% mortality follow-up. Cause-specific mortalities were classified using ICD-9 codes.

For the statistical analysis, the study authors performed direct standardization by age, given that bone Pb is strongly associated with age. The standardization was achieved by calculating a weighted average of the age-specific averages (continuous variables) or percentages (in 5-year groups). The authors used multivariable Cox proportional hazard regression to estimate hazard ratios and 95% confidence intervals (CIs). Tests for linear trend across tertiles were computed by including the tertile of Pb biomarkers as a continuous variable in the models. Non-linearity of Pb terms was also tested with penalized spline terms for the Pb biomarkers.

In multivariable adjusted analysis, all-cause, cardiovascular, and ischemic heart disease deaths showed significant associations with patella Pb. Among categories of cardiovascular deaths, the multivariable-adjust HR for mortality from ischemic heart disease was significantly elevated in the highest patella Pb tertile. However, there were too few ischemic heart disease deaths among participants without heart disease or stroke at baseline to allow for stable, multivariable-adjusted models of this outcome in this subset of participants. The multivariable HR for other cardiovascular deaths did not appear to increase with increasing bone Pb. The results are summarized in Exhibit 10.

In the spline regression model, there was some suggestion that the association with all-cause mortality and ischemic heart disease plateaus at higher bone Pb concentrations, although the authors note that in these ranges the data were sparse and the confidence intervals were wide. The results for tibia Pb and mortality were much weaker than those for patella Pb. Additionally, contrary to the Schober et al., Menke et al., and Khalil et al. results, no association was found between blood Pb and mortality ($p\text{-}trend > 0.05$ for all CVD deaths and for all-cause mortality) (Menke et al., 2006; Schober et al., 2006). The authors hypothesized that their results vary from the Schober et al. and Menke et al. results due to a smaller sample size (i.e., not enough power to detect a relationship) or potentially due to greater variability in lead exposure in the Greater Boston area. The variability could impact the result because with more fluctuation in blood Pb levels "any single blood lead measure would be less correlated with overall lead exposure in our cohort and show a reduced effect estimate for mortality if it is truly cumulative exposure that is important for mortality outcomes" (Weisskopf et al., 2009, p.1061)

As stated previously, personal communication with study authors revealed plans to reanalyze the data and publish a correction in *Circulation* (Personal Communication with Mark Weisskopf, 2013). Therefore, any analysis on this paper should be based on the correction when it becomes available, not the currently published paper. Further, the results, although potentially applicable to a portion of the U.S. population, may be less applicable to the entire U.S. adult population given that the cohort consisted only of older men.

Exhibit 10. Hazard Ratios and 95% Confidence Intervals for All-Cause, Cardiovascular Disease, Ischemic Heart Disease, and Other Cardiovascular by Tertile of Patella Pb at Baseline

	Tertile of Patella Pb			
	1 (<22 µg/g)	2 (22 to 35 µg/g)	3 (>35 µg/g)	*p* for trend
N	298	283	279	
follow-up, y	2763	2532	2387	
All-cause				
Deaths	55	75	111	
Crude	Reference	1.47 (1.04-2.08)	2.45 (1.77-3.39)	<0.0001
Multivariable 1[a]	Reference	1.44 (0.79-3.26)	1.76 (0.95-3.25)	0.07
Multivariable 2[b]	Reference	1.75 (0.82-3.75)	2.52 (1.17-5.41)	0.02
All cardiovascular				
Deaths	33	41	63	
Crude	Reference	1.36 (0.86-2.15)	2.33 (1.53-3.55)	<0.0001
Multivariable 1[a]	Reference	1.39 (0.61-3.19)	2.45 (1.07-5.60)	0.03
Multivariable 2[b]	Reference	1.63 (0.51-5.18)	5.63 (1.73-18.3)	0.003
Ischemic Heart Disease (Subset of All cardiovascular)				
Deaths	14	18	30	
Crude	Reference	1.41 (0.70-2.85)	2.69 (1.42-5.08)	0.002
Multivariable 1[a]	Reference	2.99 (0.40-22.6)	8.37 (1.29-54.4)	0.01
Other Cardiovascular (Subset of All cardiovascular)				
Deaths	19	23	33	
Crude	Reference	1.31 (0.72-2.41)	2.07 (1.18-3.64)	0.01
Multivariable 1[a]	Reference	1.01 (0.38-2.70)	1.16 (0.40-3.39)	0.79
Multivariable 2[b]	Reference	0.64 (0.15-2.80)	1.35 (0.30-6.09)	0.73

[a] Adjusted for age, smoking (never/former/current and pack years), and education.
[b] Same model but excluding the 154 participants (53 death) who had heart disease (146) or stroke (11) at baseline.
Source: Weisskopf et al. (2009)

3.5 Summary of Study Selection

A summary of the rationale for our study selection for the estimation of the concentration-response function is available in Exhibit 11. Menke et al. (2006) estimated a continuous function and used the largest sample size and the most representative adult population based on age, sex, and blood Pb levels of all studies considered. Additionally, the EPA ISA specifically pointed to the Menke et al. study as the "strongest…presently published for estimating the effects of Pb on cardiovascular disease-related mortality" (p. 5-355). The EPA ISA supported this statement by explaining that the study uses a nationally representative sample of men and women and addresses some key weaknesses of previous NHANES analyses, such as examining confounding by many factors including hypertension and kidney function (U.S. EPA, 2013).

Exhibit 11. Summary of Studies under Consideration as the Basis of the Concentration-Response Function

Study	Presentation/Use of a Continuous Concentration-Response Function in the Study?	Will Study Be Used to Develop the Concentration-Response Function?
Schober et al. (2006) *Blood lead levels and death from all causes, CVD, and cancer: Results from the NHANES III Mortality Study*	Yes	No. While the study bases some of its findings on a continuous concentration-response function, these functions were not presented in the study, and the authors were unable to retrieve them.
Menke et al. (2006) *Blood lead below 0.48 µmol/L (10 µg/dL) and mortality among US adults*	Yes	Yes. The study presented results of an increase in CVD mortality risk as a result of a continuous increase in blood Pb level (3.4-fold increase) for adults age 20 and above.
Khalil et al. (2009) *Association of blood lead concentrations with mortality in older women: a prospective cohort study*	No	No. While results support the association between Pb exposure and mortality, the study does not present or use a continuous concentration-response function. Additionally, the results may be less applicable to the general adult population.
Weisskopf et al. (2009) *A prospective study of bone lead concentration and death from all causes, CVD, and cancer in the Department of Veterans Affairs Normative Aging Study*	No	No. The study does not present or use a continuous concentration-response function. Additionally, the results may be less applicable to the general adult population. Finally, the study authors recommended against using the results until a correction is published.

Exhibit 12 summarizes the populations used and the key findings for the four studies, all of which used Cox proportional hazards models to derive their hazard ratios. Examining this exhibit reveals potential explanations as to why Schober et al. (2006) and Menke et al. (2006), although both using NHANES III data, came up with different effect estimates—they used different subsets of the NHANES dataset, used different ICD codes to code for CVD mortality, and controlled for different variables. Menke also used a more inclusive set of participants, including adults age 20 and above, while Schober et al. focused on adults age 40 and above.

Exhibit 12 also shows that Khalil et al. (2009) did not find a statistically significant relationship between blood Pb and CVD mortality in their older population of women with a higher mean blood Pb level. It is possible that the only reason Khalil et al.'s (2009) estimates were not statistically significant was due to a lack of power (i.e., a smaller number of subjects in their study population).

Weisskopf et al. (2009) did not find a statistically significant relationship between blood Pb and CVD mortality, though they did find a statistically significant relationship when bone is the measure of Pb exposure. Selection bias may be one cause for the lack of an association between blood Pb and CVD mortality. Selection criteria for the Normative Aging Study are heavily weighted toward individuals without CVD, given that in order to be entered into the cohort an individual could not have prior CVD. For older individuals this creates a strong selection bias toward heart-healthy people (Weisskopf, 2013). Further, there were fewer than 700 subjects in the Weisskopf et al. (2009) analysis of CVD mortality, potentially leading to a lack of power to detect an association. In addition, as pointed out in the Weisskopf et al. (2009) discussion, the lack of a finding may be due to greater variability in lead exposure in the Greater Boston area. The variability could impact the result because with more fluctuation in blood Pb levels, "any single blood lead measure would be less correlated with overall lead exposure in our cohort and show a reduced effect estimate for mortality if it is truly cumulative exposure that is important for mortality outcomes" (Weisskopf et al., 2009, p. 1061). The difference in findings based on the biomarker of exposure in the study may be a result of exposure misclassification. It is possible that bone may be the more accurate measure of Pb exposure in relation to cardiovascular disease mortality risk and the exposure misclassification may not be as prominent of an issue with bone Pb. Alternatively, it may be that a stronger association is measured between bone lead and cardiovascular disease which may explain why a statistically significant association was found when using bone Pb as the biomarker of exposure but not when using blood Pb. However, the authors have cautioned that a correction to the analysis is forthcoming, and that results from the 2009 study should not be used.

Due to heterogeneity across the four studies in terms of population, health effect (ICD codes), and Pb reference level, as well as the overlap in study populations between Menke et al. and Schober et al., it is not appropriate to synthesize the blood Pb hazard increase estimates from these studies quantitatively, for example using meta-analysis.

Exhibit 12. Summary Statistics for Studies Considered as the Basis for the Concentration-Response Function Relating Blood Pb Levels to Cardiovascular Disease-Related Mortality

Study	Population Examined	Mean Pb Level[a]	ICD Codes	Reference Level[a]	Pb Level[a]	Hazard Increase (95% CI)
Khalil et al. (2009)	533 women aged 65-87 years enrolled in the Study of Osteoporotic Fractures	5.3 ± 2.3 µg/dL	ICD9: 425, 429.2, 440-444, 428, 401-404, 410-414, 430-438, and 798	<8µg/dL	> 8 µg/dL	1.78[b] (0.92-3.45)
Menke et al. (2006)	13,946 NHANES III participants ≥ 20 years of age	2.58 µg/dL (geometric mean)	ICD-9: 390 – 434; 436 - 459; ICD-10: I00-I99	<1.94 µg/dL	1.94-3.62 µg/dL	1.03 (0.69-1.55)[c]
					>3.62 µg/dL	1.55[c] (1.08-2.24)
				1.46 µg/dL (20th percentile)	4.92 µg/dL (80th percentile)	1.53[c] (1.21-1.94)
Schober et al. (2006)	9,686 NHANES III participants ≥40 years of age	Median: 4.14 µg/dL[a]	ICD-10: I00–I78	<5 µg/dL	5-9 µg/dL	1.20[d] (0.93-1.55)
					>10 µg/dL	1.55[d] (1.16-2.07)
Weisskopf et al. (2009)	Men from the VA Normative Aging study n = 860 for patella Pb; n = 863 tibia Pb; and n = 1,235 blood Pb)	Patella Pb: 31.2 µg/g Tibia Pb: 21.8µg/g Blood Pb: 4.8 µg/dL (geometric mean)	ICD-9 codes: 390 to 459	Patella Pb: < 22 µg/g	Patella Pb: >35 µg/g	5.63[e] (1.73-18.3)
				Blood Pb: <4 µg/dL	Blood Pb: >6 µg/dL	0.69[f] (0.33-1.47)

Study	Population Examined	Mean Pb Level[a]	ICD Codes	Reference Level[a]	Pb Level[a]	Hazard Increase (95% CI)

[a] Reported values reflect blood Pb levels unless stated otherwise.

[b] This model was adjusted for age, clinic where examination occurred, BMI, education, smoking, alcohol intake, estrogen use, hypertension, walking for exercise, diabetes, and total hip bone density.

[c] This model was adjusted for age, race-ethnicity, sex, diabetes, BMI, current or former smoking, alcohol consumption, physical activity, low income, CRP, total cholesterol, high school education, urban residence, postmenopausal status, hypertension and level of kidney function.

[d] This model was adjusted for sex, race/ethnicity, education, and smoking status.

[e] This model was adjusted for age, smoking (never/former/current and pack years), and education. It also excluded the 154 participants who had heart disease or stroke at baseline (n=706).

[f] This model was adjusted for age, smoking (never/former/current and pack years), and education. It also excluded the 212 participants who had ischemic heart disease, or stroke at baseline (n= 648).

4. Derivation of Blood Pb Concentration-Response Function

As discussed in Section 3.5, Menke et al. (2006) is the best study to use for the estimation of the concentration-response function due to its underlying continuous concentration-response function and applicability to the adult general population.

Exhibit 7 shows the multivariate adjusted relative hazards of CVD mortality, with 95% CIs, based on a Cox proportional hazards model using the log of the blood Pb level. We calculated HRs for the difference between the (log-transformed) 80th and 20th percentiles of the blood Pb distribution given in the study. If blood Pb level had not been log-transformed first, the concentration-response relationship between blood Pb level and mortality resulting from the Cox proportional hazards model would be log-linear in form (i.e., the natural log of mortality would be a linear function of blood Pb level). Since Menke et al. (2006) log-transformed blood Pb level before estimating the Cox proportional hazards model, however, the resulting concentration-response relationship between blood Pb level and mortality is log-log in form (i.e., the natural log of mortality is a linear function of the natural log of blood Pb level).

The basic form of the concentration-response function underlying the HRs presented in Exhibit 7 is

$$\ln(y) = \alpha + \beta * \ln(x)$$

or

$$y = B * x^{\beta} \qquad (1)$$

Where:

$B = e^{\alpha}$,

where y is the probability of the adverse health effect (e.g., CVD mortality), α includes the other independent variables in the model and x is *blood Pb level*.

This concentration-response relationship could be used in a health impact function as follows. If y_0 denotes the baseline probability of the health effect when *blood Pb level* is at baseline level x_0 and y_1 denotes the (lower) probability of the health effect associated with a (lower) *blood Pb level* of x_1 (the blood Pb level associated with a rule), then it can be shown that the reduced risk of the health effect, $\Delta y = (y_0 - y_1)$, associated with a change in *blood Pb level* from x_0 to x_1 is:

$$\Delta y = y_0 * [1 - \left(\frac{x_1}{x_0}\right)^{\beta}] \; . \qquad (2)$$

If *pop* denotes the population for whom this change in *blood Pb level* occurs, then the number of avoided cases of the health effect is

$$cases\ \ avoided\ = y_0 * [1 - \left(\frac{x_1}{x_0} \right)^{\beta}] * pop\ . \qquad (3)$$

The coefficient (estimate of β) and the standard error for CVD mortality for the overall population are 0.35 (0.10).[6] Menke et al. noted that subgroup interaction terms were not statistically significant, supporting the use of the coefficient for the overall population in the remainder of this analysis. Adjustment in the analysis included age, race-ethnicity, sex, hypertension, diabetes, BMI, current or former smoking, alcohol consumption, physical activity, low income, C-reactive protein, total cholesterol, level of kidney function, high school education, urban residence, and post-menopausal status.

The CVD mortality probability associated with every value of x_0 is not available, and therefore to apply this function we will use the baseline incidence rate (or, equivalently, the baseline per-person probability of CVD mortality) for the adult general population, regardless of starting blood Pb level, for y_0, which is standard practice for this type of analysis (U.S. EPA, 2008c, 2012a). This assumption will overstate the probability of CVD mortality for some people and will understate it for others. It is generally assumed that these over- and underestimates of risk will largely cancel each other out when the number of cases of CVD mortality avoided in the exposed population are calculated (U.S. EPA, 2008c, 2012a). The CDC has data on mortality rates at various age ranges down to the county level in the National Vital Statistics System (CDC, 2012a). For the purpose of the benefits analysis, we could apply different baseline CVD mortality rates throughout the United States at the county, city, or state level, resulting in more precise estimates than applying one baseline CVD mortality rate to the entire country.

[6] Drs. Menke and Guallar, two of the study authors, sent us the coefficients (betas), and their standard errors, in the log-log concentration-response functions for both all-cause mortality and CVD mortality underlying the HRs and 95% CIs shown in Figure 2 of their study and Exhibit 77 in the previous section. We were also able to back-calculate these values from the published results, and our back-calculated coefficients matched the coefficients that Drs. Menke and Guallar sent us, confirming our understanding of the form of the underlying concentration-response functions.

5. Generalizability of the Concentration-Response Function from Menke et al.

In order for the concentration-response function to be most useful in a benefits analysis, it should be generalizable to a large portion of the population. To properly use the concentration-response function derived in the previous section, the function must be applied to the appropriate population (Section 5.1) and the appropriate blood Pb concentrations (Section 5.2), and over the appropriate time span (Section 5.3). With these considerations, sample calculations presenting the benefits based on a hypothetical example are shown in Section 5.4.

5.1 Generalizability to the Adult Population

As noted in Exhibit 9, effect estimates were derived for many subsets of the populations (e.g., smokers, diabetics, individuals over 60). Given that the Menke et al. (2006) findings of statistical significance for the CVD mortality endpoint persisted after the adjustment for many confounders (see Exhibit 5) and tests for the interaction for between blood Pb levels and different subgroups resulted in no statistically significant relationships, it is appropriate to use the beta estimate for the entire population in Equation 3. Therefore, the function can be applied to adults generally.

5.2 Range of Blood Pb Levels over Which the Concentration-Response Function Should Be Applied

The blood Pb levels analyzed in Menke et al. (2006) also merit special consideration. While the geometric mean blood Pb level of 2.58 µg/dL reported in Menke et al. is low relative to other published studies, blood Pb levels have continued to decline in the decades since the data were collected (1988-1994), falling to a geometric mean of 1.09 µg/dL in 2011-2012 (see Exhibit 15) (CDC - National Center for Health Statistics, 2013). This raises the question of whether a concentration-response function based on the Menke study should be applied to populations with lower mean blood Pb levels than those reported in the study – i.e., should the function be applied to all blood Pb levels in the population or only to those blood Pb levels exceeding a specified value.

5.2.1 Apply Study to All Blood Pb Levels

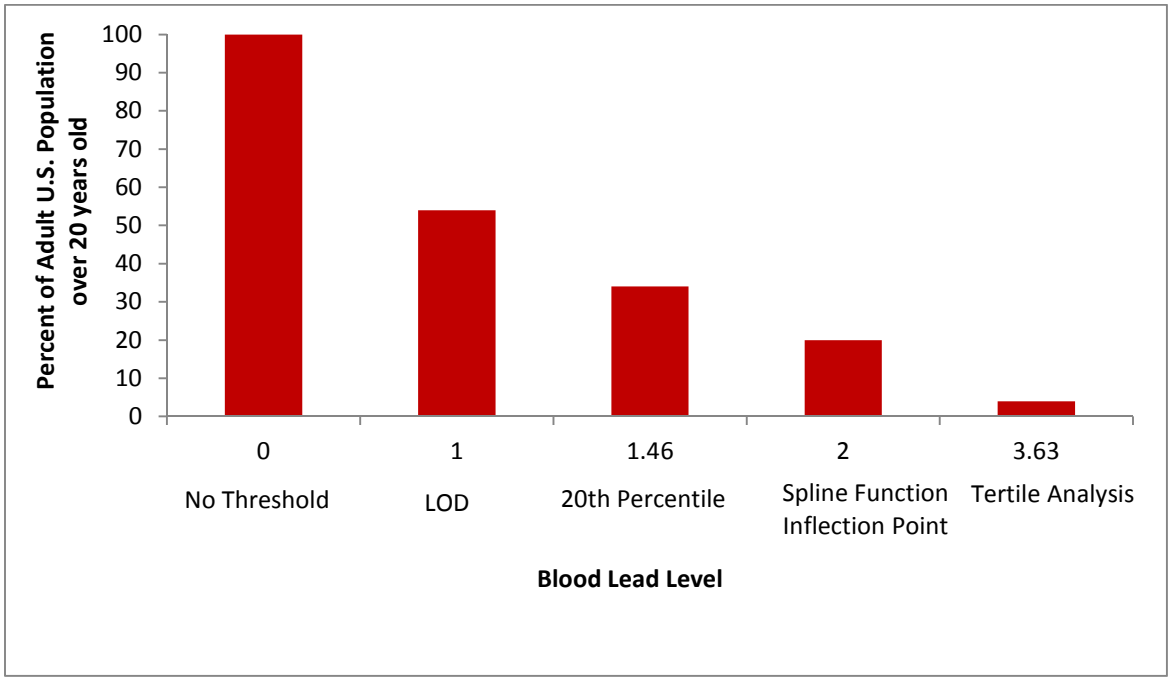
One option is to apply the function from Menke et al. (2006) to the entire population, regardless of blood Pb level. The arguments for this conceptual model are based on a couple of factors. The first factor is that no threshold has been identified for adverse effects of Pb exposure. This has been demonstrated in both the toxicologic and epidemiologic literature (U.S. EPA, 2013) and is further evidenced by the fact that the hazard ratio presented in Exhibit 7 is based on the log-blood Pb increase, with blood Pb being a continuous variable without a threshold in a linear model. Therefore, for every 3.4-fold increase, regardless of where on the concentration-response curve the blood Pb level falls, the increase in hazard for CVD mortality is 53% (95% CI: 21%–94%). The second factor is that when quantifying benefits, this assumption ensures that no one is missed in the benefits evaluation. There is precedent in other EPA assessments for taking this approach, such as when quantifying IQ loss from blood Pb exposure in children in the National Ambient Air Quality standards (NAAQS). Benefits were estimated below the lowest measured blood Pb level of 1.47 µg/dL in the Lanphear model (U.S. EPA, 2008b).

5.2.2 Apply Study to Blood Pb Levels Exceeding a Certain Value

It can be argued that applying the Menke et al. (2006) function to all individuals regardless of blood Pb level may not be appropriate, that the concentration-response function should be used only over the range of levels assessed in the study, or applied only to those with blood Pb levels above some other cutoff level. With environmental data, there is often censoring to the left at the limit of detection (LOD). Thus, it could be argued that the concentration-response function may be applied at levels above the LOD (i.e., 1 µg/dL). There may also be other cutoff points such as applying the function only above the 20th percentile (i.e., 1.46 µg/dL), above the inflection point from the Menke et al. spline functions (i.e., 2 µg/dL) or above the third tertile of Menke et al.'s tertile analysis (i.e., 3.63 µg/dL). The reasoning for and against using each of several different cutoff points based on results from the Menke et al. study are provided below.

One issue with using a cutoff level is that potential benefits will be missed in populations with blood Pb levels below this level. For example, only 20% of U.S. adults currently have blood Pb levels above 2 µg/dL. This is demonstrated in Exhibit 13, which shows several potential thresholds one could use for this analysis and the corresponding proportion of the population to which the benefits would be limited if each threshold were used.

Exhibit 13. Proportion of the Population included in Benefits Analysis Based on Various Cutoff Points



Source: National Health and Nutrition Examination Survey (NHANES) 2011-2012.

Greater Than 1 µg/dL

For NHANES III, the cohort examined in the Menke et al. (2006) analysis, the blood Pb LOD was 1 µg/dL. In their analysis, the concentration of any sample below this LOD (for 8.1% of study

participants) was replaced with a concentration of 0.7 µg/dL (Menke et al., 2006), introducing measurement error into the data at low blood Pb levels. It is unlikely that all samples below the LOD have the same concentration; instead, there is a distribution of levels between 0 and the LOD (Belova, Greco, Riederer, Olsho, & Corrales, 2013). Because reliable estimates of blood Pb in Menke et al. (2006) are available only at levels above the LOD, it can be argued that the regression coefficient should instead be applied only to individuals with blood Pb levels above the LOD of 1 µg/dL. This is consistent with what was done for children's IQ in EPA's Renovation and Repair Rule (U.S. EPA, 2008a).

Greater Than 1.46 µg/dL

Given that the hazard ratio (see Exhibit 7) was based on a comparison of those with a blood Pb level of 4.92 µg/dL (80th percentile) to those with a blood Pb level of 1.46 µg/dL (20th percentile), another potential cutoff point is 1.46 µg/dL. It should be recognized that this cutoff point is based on an arbitrary comparison, the 20th to 80th percentile from which the hazard ratio was developed. The hazard ratio could have been developed based on a comparison of any two blood Pb levels within the range of blood Pb levels from the study.

Greater Than 2 µg/dL

Menke et al. (2006) present the results from spline regression models that demonstrate an increase in all-cause and myocardial infarction (MI) deaths; both of these models have an inflection point at approximately 2 µg/dL(0.1 µmol/L; Exhibit 6). That is, the spline figure shows negative slopes between 0 and 2 µg/dL for risks of all-cause and MI deaths. It should be noted that the 20th percentile blood Pb level in Menke et al. was 1.46 µg/dL, suggesting that there may have been low power below 2 µg/dL. Additionally, as mentioned previously, the LOD in the sample was 1 µg/dL and any concentration below 1 µg/dL was assigned 0.7 µg/dL. The authors state that 8.1% of participants were below this level. The smaller sample size in this area of the graph, along with the measurement uncertainty due to the measurements below the LOD in this region, could contribute to the counterintuitive sign seen in Menke et al.'s (2006) spline model analysis for myocardial infarction and all-cause mortality below 2 µg/dL (see Figure 1 of Menke et al., 2006).

It should be noted when considering this cutoff point that Menke et al. also estimated a spline function for stroke mortality and this function does increase monotonically with blood Pb above 1 µg/dL. Total CVD-related mortality, the endpoint we are examining in this report, is not included in the figure, and therefore it is not known whether the same relationship exists for CVD mortality as in the MI, all-cause, or stroke spline functions.

Last, the 0.35 coefficient for CVD mortality was derived using data from the entire distribution of blood Pb levels in the study. If the inflection point of 2 µg/dL in the MI and all-cause mortality spline functions also holds for CVD mortality, 0.35 may underestimate the relationship between blood Pb increase and CVD mortality risk for individuals with blood Pb above 2 µg/dL.

Greater Than 3.63 µg/dL

Menke et al.'s tertile analysis found a positive, but not statistically significant, difference between the risk of CVD mortality in the second tertile (1.93–3.62 µg/dL) when compared to the first tertile (<1.93 µg/dL). Statistical significance in the tertiles was detected only when comparing the third tertile (≥ 3.63 µg/dL) to the first tertile (see Exhibit 5). Therefore, it could be argued that the

concentration-response function derived from the continuous analysis in Menke et al. (2006) should only be applied to individuals with blood Pb levels greater than or equal to 3.63 µg/dL. However, in the trend analysis of the tertiles, Menke et al. did find a statistically significant increase across these three categories, and the hazard ratio from which our function is derived is developed without a threshold. In addition, the lack of a significant difference between the first two tertiles could be driven by the inflection point around 2 µg/dL seen in the MI and all-cause mortality spline functions. If CVD mortality exhibits a similar functional form, then it is unsurprising that CVD mortality risk from the first two tertiles would not be statistically significantly different on average because the upward trend in the blood Pb-CVD mortality relationship only begins around 2 µg/dL.

5.3 Issues Regarding the Profile and Measurement of Lead Exposure and Risk

Questions still remain about the time frame over which the biomarker most accurately represents risk. As stated by the EPA ISA, "uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies" (U.S. EPA, 2013, p. 1xxxv). These uncertainties are not addressed by Menke et al. (2006) or any of the other epidemiologic studies we examined. This is because all of the findings are based on a single biomarker (blood or bone) measurement per study subject. Therefore, there is no clear answers to issues regarding cessation lag and latency,[7] and there is uncertainty in which conceptual model best represents the relationship between the biomarkers or Pb exposure and current risk of CVD mortality. The main conceptual models are:

1. Current CVD mortality risk = f(current blood Pb)

2. Current CVD mortality risk = f(average blood Pb over *X* years)

3. Current CVD mortality risk = f(average blood Pb over *X* years) + latency

4. Current CVD mortality risk = f(peak blood Pb)

5. Current CVD mortality risk = f(current bone Pb)

6. Current CVD mortality risk = f(average bone Pb over *X* years)

7. Current CVD mortality risk = f(average bone Pb over *X* years) + latency

8. Current CVD mortality risk = f(peak bone Pb)

where current CVD mortality risk represents the CVD mortality risk within the next *y* years and where *X* years can include years in the follow up period, in addition to past years. Additionally, *X* could be many values, even less than a year. Other conceptual models that incorporate multiple peaks or different biomarkers are also possible.[8]

[7] See U.S. EPA (2010) for definitions of *latency* and *cessation lag*.

[8] Note that Models 1 and 2 can be considered special cases of Model 3 in which latency is set equal to zero. Similarly, Models 5 and 6 can be considered special cases of Model 7.

Using Menke et al. (2006) assumes that conceptual model 1 in the above list is true. This is because the Menke et al. study used an individual's current blood Pb level to model the potential relationship between blood Pb and CVD mortality and because they used the Cox regression model to model this relationship. The Cox regression model assumes that the hazard ratio will be the same regardless of the follow-up time frame. An inherent assumption of the Cox model, known as the proportional hazards assumption, is that an effect of a variable (main exposure or covariate) does not change over time (i.e., the hazard ratio is a fixed constant over time). Though hazard rates may vary with time, the hazard ratio will always be the same because the proportionality assumption is met and time is cancelled out when the ratio is calculated (Allison, 2000; Tibshirani, 1982).

In conceptual models 2 and 3 it is unclear if the health impact function would over- or underestimate the number of cases. The Menke et al. (2006) analysis is based on a single blood Pb measurement per individual, which is reflective of both recent exposures (<30 days) from exogenous sources and past exposures (years to decades) that had been stored in tissues (e.g., bone) and released endogenously (National Toxicology Program, 2012; U.S. EPA, 2013). Therefore, this point-in-time estimate may be higher or lower than an individual's average exposure over a specified period of time, depending on the individual's exposure profile and other physiological characteristics that may contribute to the release of Pb from bone.

In conceptual model 4, if peak exposures are most important in predicting risk, it would be hard to predict in which direction the results will be biased because we do not know when the NHANES measurements were taken in relation to the timing of the peak exposure. External exposures are represented in blood Pb for about 30 days, during which Pb is eliminated or stored in bone, and therefore the spot blood Pb sample would not be likely to capture the higher blood Pb concentration as a result of the external exposure spike, unless it occurred within the last 30 days.

If the conceptual models that incorporate latency (3 and 7 from the above list) are correct, using Menke et al.'s results as the basis of our health impact function is likely to overestimate the monetized (i.e., dollar-valued) benefits that would result from any rule that decreases Pb exposure. This is because benefits would be realized later than predicted when not considering latency. Since benefits in the future are discounted, ignoring latency (and not discounting benefits) would result in an overestimation of monetized benefit. In benefits estimation, an assumption about latency could be built in to a sensitivity analysis.

If risk is more accurately represented by bone Pb (conceptual models 5 through 8), which is thought to be a better marker for cumulative Pb exposure, the health impact function may underestimate the benefits. If bone is the more accurate measure and if using blood Pb as a proxy measurement for bone Pb adds random, non-biased error, using bone Pb should result in less exposure misclassification than using blood Pb. Therefore, using blood Pb may bias the result toward the null. That is, a single blood Pb measurement is highly variable, and therefore using the highly variable measurement to predict an outcome that may be a consequence of a long-term exposure results in an underestimation of the true effect.

Also, for all of the conceptual models, the data are not sufficiently detailed to indicate whether several short periods of high exposure would impact an individual differently from a continuous lower level of exposure. It would be difficult to separate these two scenarios given that they may

result in the same cumulative average exposure (which can be represented by the bone Pb measurement). Additional information on bone and blood Pb biomarkers is provided in Appendix B.

The concentration-response function derived from Menke et al. (2006) was estimated with a static version of the Cox proportional hazards model. That is, Menke et al. (2006) explored the relationship between the level of blood Pb measured at a certain date and whether the study participant died between the date of blood sample collection and December 31, 2000. Because exposure is represented by a static/point-in-time measurement, this type of modeling cannot answer questions about the existence of risk cessation lag. Dynamic survival models could be used to explore the idea of cessation lag in this context, but they will require information on the exposure time profile (e.g., blood Pb measurements at several points in time). The current literature does not contain this type of analysis.

5.4 Sample Benefits Calculation

To gain an understanding of the magnitude of the benefits that would result from using the function derived in Section 4, we present hypothetical examples. Recall from the previous section that Equation 3, the health impact function based on the Menke et al. concentration-response function, is:

$$cases\ avoided = y_0 * [1 - \left(\frac{x_1}{x_0}\right)^{\beta}] * pop \cdot \qquad (3)$$

Where:

y_0 = CVD disease mortality rate

x_1 = blood Pb level with rule

x_0 = blood Pb level without rule

β = 0.35 (SE = 0.10) (from Menke et al., 2006)

pop = U.S. adult population over 20 years old

The hypothetical examples presented in this section represent a decrease in short-term exposure spikes from an event such as a renovation.

5.4.1 Cardiovascular Disease Mortality Rate

We use various inputs for each of the parameters outlined in Equation 3 except for y_0, the baseline cardiovascular disease mortality rate. For the hypothetical example calculations, we use the age (within 10 years) and gender specific CVD mortality rates represented in Exhibit 14, for all scenarios.

Exhibit 14. Cardiovascular Disease-Related Mortality in the United States in 2010

Age (years)	Gender	Number of Deaths	CVD Mortality Incidence, Y_0
20-29	M	1,562	7.2E-05
	F	780	3.7E-05
30-39	M	4,867	2.4E-04
	F	2,491	1.2E-04
40-49	M	18,005	8.3E-04
	F	8,644	3.9E-04
50-59	M	45,207	2.2E-03
	F	20,220	9.4E-04
60-69	M	64,548	4.6E-03
	F	35,298	2.3E-03
70-80	M	93,258	1.2E-02
	F	75,440	7.6E-03
Total (20-80 years)	**M**	**227,447**	**2.2E-03**
	F	**142,873**	**1.3E-03**
	Both	**370,320**	**1.7E-03**

Source: CDC – National Center for Health Statistics (2010)

5.4.2 Blood Pb Levels

For the ratio of with and without rule blood Pb levels ($\frac{X_1}{X_0}$) we plan to take two approaches, one that assumes all individuals experience the same *percentage* change in their blood Pb level as a result of the rule and one that assumes all individuals experience the same *absolute* change as a result of the rule. Both of these approaches are oversimplifications, as each individual in reality may have different exposure patterns, but they are applied here for illustrative purposes.

As discussed in the previous section, it is unclear from the available data if peak blood Pb levels or average blood Pb levels are more important in regard to the risk of cardiovascular disease mortality. Therefore, to examine how benefits from a rule may vary based on the average or peak blood Pb level, we will use two values, 0.05 µg/dL or 1 µg/dL above the current geometric mean levels from the most recent NHANES analysis (see Exhibit 15) for the appropriate age and gender category.[9] That is:

[9] For this hypothetical example we are making simplifications to focus on the concentration-response function, and understand that modeling blood Pb changes is not trivial; however, that discussion is beyond the scope of this report.

$x_0 = 0.05 + BLL_b$ or

$x_0 = 1.00 + BLL_b$

Where:

BLL_b = the geometric mean blood Pb level from NHANES, see Exhibit 15

The 0.05 µg/dL increase over the current geometric mean blood Pb levels represents the average blood Pb levels over the course of an event such as a renovation, whereas the 1 µg/dL increase represents a potential peak increase in blood Pb level. Then, assuming the rule negates all potential exposure from an event such as a renovation, we calculate x_1 to be x_0 minus the increase in exposure caused by the renovation, either 0.05 µg/dL or 1 µg/dL. That is:

$x_1 = x_0 - 0.05 = BLL_b$ or

$x_1 = x_0 - 1.00 = BLL_b$

For the *percentage* increase we will use the equations below to examine the sensitivity of the results to the ratio of baseline to post-rule blood Pb levels.

That is:

$x_0 = BLL_b * 1.05$ or

$x_0 = BLL_b * 1.50$, and

$x_1 = BLL_b$

In the case of a rule that would decrease ambient Pb exposure levels, x_0 and x_1 would be calculated differently. We would assume that x_0 is equal to the current baseline blood Pb levels and x_1 is equal x_0 minus a specified decrease in blood Pb levels. That is, instead of assuming we are avoiding an increase in blood Pb level, as we are for an event in this LRRP-type rule, we would assume we are decreasing blood Pb levels.

Exhibit 15. Adult Blood Lead Levels in 2011-2012

Age (years)	Gender	Geometric Mean	Std. Error	75th Percentile	95th Percentile	Percentage above:			
						1 µg/dL	1.46 µg/dL	2 µg/dL	3.62 µg/dL
20-29	M	0.93	0.05	1.29	2.85	37%	19%	10%	4%
	F	0.56	0.02	0.74	1.43	11%	5%	2%	0%
30-39	M	1.00	0.04	1.44	2.52	46%	24%	11%	1%
	F	0.62	0.03	0.86	1.61	16%	6%	3%	1%
40-49	M	1.25	0.05	1.74	3.64	60%	36%	18%	5%
	F	0.93	0.03	1.28	2.48	39%	17%	9%	2%
50-59	M	1.61	0.10	2.24	5.20	76%	52%	30%	8%
	F	1.23	0.04	1.78	2.73	63%	35%	16%	3%
60-69	M	1.78	0.09	2.61	4.60	85%	59%	39%	13%
	F	1.28	0.08	1.76	3.10	66%	39%	15%	4%
70-80	M	1.86	0.07	2.65	4.02	89%	68%	42%	10%
	F	1.45	0.06	2.13	4.00	72%	49%	28%	7%
All 20+	M	1.31	0.04	1.94	4.00	63%	40%	23%	6%
	F	0.93	0.03	1.42	2.76	43%	24%	12%	3%
	Both	1.09	0.03	1.67	3.36	52%	32%	17%	4%

Source: National Health and Nutrition Examination Survey (NHANES) 2011-2012.

5.4.3 Population

For this example we assumed that 0.5% of the population (approximately 1 million people) is impacted by the rule. We also stratified our analysis because, as discussed in Section 5.2.2, in certain cases it may be appropriate to apply the function only above different cutoff levels of blood Pb. For illustrative purposes, we apply the function to the entire population affected by the rule and then restrict the benefits to only the proportion of the population that has blood Pb concentrations greater than 1, 1.46, 2, and 3.63 (see Exhibit 15). We calculated the following parameters for each stratification level:

- We calculated mean blood Pb levels (BLL_b) as geometric means of blood Pb levels from NHANES 2011-2012, for only those with blood Pb levels above the starting level of interest.
- We multiplied the affected population (*pop*) by the share of the population with blood Pb levels above the cutoff level of interest, based on NHANES 2011-2012.
- We calculated the without-rule blood Pb level (x_0) in two ways. For percentage changes, we calculated 5% and 50% increases in our estimates from mean blood Pb levels (x_1). For absolute changes, we added 1.0 µg/dL and 0.05 µg/dL to each NHANES participant's blood Pb level, and then calculated the geometric means for each stratification. We used these geometric means as x_0 in the function.

5.4.4 Beta

Lastly, the central estimate of beta is 0.35 µg/dL (SE=0.10). In order to understand the sensitivity of the results to the value of this parameter, we will run all of our model estimates with the central estimate of beta and the upper bound (β = 0.55) and lower bound (β = 0.15) of the 95% confidence interval.

5.4.5 Summary of Inputs

A summary of the various inputs we use to calculate benefits for various hypothetical examples are presented in Exhibit 16.

Exhibit 16. Input Parameters for a Hypothetical Benefits Analysis

Parameter	Assumption
CVD mortality rate, y_0	Age (within a 10-year range) and gender-specific CVD disease mortality rates (ICD-9 codes 390-434 and 436-459; ICD-10 codes I00-I99) (see Exhibit 14).
Blood Pb levels, x_1,x_0	Two approaches will be taken: • A percent increase (approximately 5% or 50%): ○ x_0 = NHANES geometric mean blood Pb multiplied by 1.05 or 1.50 ○ x_1 = NHANES geometric mean blood Pb • An absolute change: ○ x_0 = NHANES geometric mean blood Pb plus 0.05 µg/dL or 1 µg/dL ○ x_1 = NHANES geometric mean blood Pb
B	0.35 (SE = 0.10) (from Menke et al., 2006)
Population	• For LRRP-type rule, 0.5% of the population or approximately 1 million people • Blood Pb cutoffs: ○ >1 ○ >1.46 ○ >2 ○ >3.63

For this hypothetical example we assume that all benefits will be experienced within 1 year. This is based on the observation that blood Pb declines rapidly following short-term elevated exposures in individuals with relatively low blood Pb levels, even though bone Pb and total body burden decline much more slowly (Figure 3-11, U.S. EPA, 2013). Further refinements of this analysis could instead use predicted blood Pb levels from a biokinetic model such as Leggett (Cal OEHHA, 2013; Leggett, 1993) to estimate changes in blood Pb over the length of time blood Pb is estimated to remain elevated relative to baseline levels.

In situations where blood Pb levels in a population are higher for longer periods of time, and a proposed rule is anticipated to reduce these levels significantly, it may take more time for the blood Pb levels to decrease due to the contribution of body burden (bone stores) on blood Pb levels. In this case, it may be more appropriate to consider a more nuanced approach to estimating the benefits than these hypothetical examples.

5.4.6 Results

Using Equation 3 along with the assumptions and data points outlined in the preceding sections and Exhibit 16, we calculated the total number of CVD mortality cases avoided under the different scenarios. By multiplying the number of cases by a value of a statistical life (VSL) in 2012 dollars of $8.43 million ($4.799 million in 1990 USD with an inflation factor of 1.76), (Bureau of Labor Statistics, 2013; U.S. EPA, 2010), we calculated the total annual benefits. These results are summarized in Exhibit 17 and Exhibit 18. The benefits of an LRRP-type rule affecting approximately 1 million people range from $1.9 million, with a 0.05 µg/dL decrease in blood Pb in individuals with blood Pb levels greater than 3.62 µg/dL and the lower estimate of beta, to $4.02 billion, with a 1 µg/dL decrease in blood Pb when considering all individuals regardless of blood Pb with the upper beta estimate.

Exhibit 17. Quantified Benefits from Absolute Change for Varying Blood Pb Cutoff Levels for LRRP Type Rule

Blood Pb Cutoff (µg/dL)	Gender	0.05 µg/dL decrease						1.0 µg/dL decrease					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L[1]	C[2]	U[3]	L	C	U	L	C	U	L	C	U
None[4]	M	5.80	13.49	21.12	$48.90	$113.70	$178.00	82.68	183.53	274.59	$697.00	$1547.10	$2314.80
	F	4.69	10.90	17.06	$39.60	$91.90	$143.80	62.27	136.82	202.73	$525.00	$1153.40	$1709.00
	Both	10.50	24.39	38.18	$88.50	$205.60	$321.80	144.96	320.35	477.32	$1222.00	$2700.50	$4023.80
1	M	3.71	8.64	13.54	$31.30	$72.80	$114.10	57.05	127.69	192.59	$481.00	$1,076.40	$1,623.50
	F	2.09	4.87	7.63	$17.60	$41.00	$64.30	31.65	70.59	106.09	$266.80	$595.10	$894.30
	Both	5.81	13.51	21.17	$48.90	$113.90	$178.40	88.71	198.28	298.67	$747.80	$1,671.50	$2,517.80
1.46	M	2.13	4.96	7.79	$18.00	$41.90	$65.60	34.42	77.54	117.72	$290.10	$653.70	$992.40
	F	1.03	2.40	3.76	$8.70	$20.20	$31.70	16.47	37.02	56.07	$138.80	$312.10	$472.70
	Both	3.16	7.37	11.55	$26.70	$62.10	$97.40	50.89	114.57	173.79	$429.00	$965.80	$1,465.10
2	M	1.04	2.42	3.80	$8.80	$20.40	$32.00	17.51	39.71	60.66	$147.60	$334.70	$511.40
	F	0.40	0.93	1.46	$3.40	$7.80	$12.30	6.71	15.19	23.18	$56.50	$128.00	$195.40
	Both	1.44	3.35	5.26	$12.10	$28.30	$44.30	24.22	54.90	83.84	$204.10	$462.80	$706.80
3.62	M	0.16	0.38	0.60	$1.40	$3.20	$5.00	2.92	6.70	10.34	$24.60	$56.40	$87.10
	F	0.06	0.13	0.21	$0.50	$1.10	$1.80	1.04	2.37	3.66	$8.70	$20.00	$30.90
	Both	0.22	0.51	0.81	$1.90	$4.30	$6.80	3.96	9.07	14.00	$33.40	$76.50	$118.00

Note: [1] L = lower beta estimate
[2] C = central beta estimate
[3] U = upper beta estimate
[4] "None" represents an unstratified analysis and includes the entire population regardless of blood Pb level

Exhibit 18. Benefits from Percentage Change for Varying Blood Pb Cutoff Levels for LRRP Type Rule

Blood Pb Cutoff (µg/dL)	Gender	5% Decrease						50% Decrease					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L[1]	C[2]	U[3]	L	C	U	L	C	U	L	C	U
None[4]	M	8.3	19.3	30.1	$69.90	$162.30	$253.80	67.1	150.5	227.3	$565.70	$1,268.40	$1,916.30
	F	5.2	12.1	18.9	$43.90	$102.00	$159.50	42.2	94.5	142.8	$355.30	$796.70	$1,203.80
	Both	13.5	31.4	49.0	$113.80	$264.30	$413.30	109.3	245.0	370.1	$921.00	$2,065.10	$3,120.10
1	M	6.8	15.7	24.5	$57.00	$132.30	$206.90	54.7	122.7	185.3	$461.20	$1,034.00	$1,562.20
	F	3.5	8.0	12.5	$29.10	$67.60	$105.80	28.0	62.7	94.7	$235.70	$528.40	$798.40
	Both	10.2	23.7	37.1	$86.10	$200.00	$312.70	82.7	185.3	280.0	$696.80	$1,562.40	$2,360.60
1.46	M	4.8	11.3	17.6	$40.90	$94.90	$148.40	39.2	87.9	132.9	$330.60	$741.30	$1,120.00
	F	2.2	5.0	7.9	$18.30	$42.60	$66.60	17.6	39.5	59.6	$148.30	$332.60	$502.50
	Both	7.0	16.3	25.5	$59.20	$137.40	$214.90	56.8	127.4	192.5	$479.00	$1,073.90	$1,622.50
2	M	3.0	7.0	10.9	$25.40	$59.00	$92.30	24.4	54.7	82.6	$205.60	$461.00	$696.50
	F	1.1	2.6	4.1	$9.40	$21.80	$34.10	9.0	20.2	30.6	$76.10	$170.60	$257.70
	Both	4.1	9.6	15.0	$34.80	$80.80	$126.40	33.4	74.9	113.2	$281.70	$631.60	$954.30
3.62	M	0.8	1.9	2.9	$6.80	$15.80	$24.60	6.5	14.6	22.1	$54.90	$123.20	$186.10
	F	0.3	0.6	1.0	$2.30	$5.30	$8.30	2.2	4.9	7.5	$18.60	$41.70	$62.90
	Both	1.1	2.5	3.9	$9.10	$21.10	$33.00	8.7	19.6	29.5	$73.50	$164.80	$249.00

Note: [1] L = lower beta estimate
[2] C = central beta estimate
[3] U = upper beta estimate
[4] "None" represents an unstratified analysis and includes the entire population regardless of blood Pb level

To put these values in perspective, according to CDC, in 2010, 1,852 individuals out of a million (0.185%) would be expected to die from CVD in the adult general population based on the CVD mortality incidence rates (CDC - National Center for Health Statistics, 2010). The absolute change examples presented avoid from 1.2% (0.05 µg/dL decrease in blood Pb) to 16% (1 µg/dL decrease in blood Pb) of CVD-related deaths, and the percentage increase examples avoid between 1.6% and 12.3% of CVD-related deaths. All of these examples are assuming the function will apply to the entire affected population regardless of blood Pb level and are based on the central beta estimate.

6. Discussion on Uncertainty and Variability in the Concentration-Response and Health Impact Functions

The hypothetical examples presented in Section 5.4 used point estimates for each of the parameters (y_0, β, and *pop*). However, in reality each of the parameters used in the function are uncertain and variable. Consequently, as with any benefits analysis, there is uncertainty and variability of the concentration-response function and the health impact function. As a result of the uncertainty in the inputs to the benefits estimation, the resulting benefits numbers are also uncertain. In this section we describe the additional sources of uncertainty and variability for both the concentration-response function (Section 6.1) and the health-impact function (Section 6.2). Where possible, we also describe approaches for characterizing the uncertainty and variability.

6.1 Uncertainty in the Concentration-Response Function

Recall from Section 4 the concentration-response function is of the form:

$$\ln(y) = \alpha + \beta * \ln(x)$$

or

$$y = B * x^{\beta}, \ (B = e^{\alpha}),$$

where y is the probability of the adverse health effect (e.g., CVD mortality), x is *blood Pb level,* and β is 0.35 (SE = 0.10), as provided by Menke et al. (2006). The uncertainty and variability associated with each of these parameters is discussed in the following sections.

6.1.1 Effect (β) Estimate

The beta estimate of 0.35 (SE=0.10) has two main uncertainties associated with it: (1) sampling uncertainty, and (2) missing data/imputation uncertainty. Sampling uncertainty is the uncertainty associated with sampling a random sample of a group as opposed to every individual in the group. This uncertainty can be characterized by using a distribution of estimates for the beta as opposed to the single value of 0.35. Based on the sampling design for NHANES III, the distribution for the beta is a t-distribution with 49 degrees of freedom (Personal Communication with Andy Menke, 2013). An example of the lower and upper bound estimates of the number of CVD deaths avoided as a result of a hypothetical situation was calculated in the previous section using the upper and lower bounds of the 95% confidence interval on the central beta estimate.

There is additional uncertainty when the estimated concentration-response function is used to make predictions for blood Pb levels below the LOD because blood Pb levels below the LOD were imputed. Unfortunately, these missing data/imputation uncertainties cannot be categorized without doing a complete reanalysis of the Menke et al. (2006) data.

As for variability associated with the β estimate, Menke et al. (2006) examined effect modification by all of the groups presented in Exhibit 7 and found no statistically significant interactions.

There is also an uncertainty in regard to the NHANES III one-time blood Pb levels, since it is unknown if they accurately represent the Pb exposure that will result in future CVD mortality cases. As stated previously, a major limitation of the Menke et al. (2006) findings is that they are based on a single blood Pb measure, which is reflective of both recent exposures (<30 days) from exogenous sources and past exposures (years to decades) that had been stored in tissues (e.g., bone) and released endogenously (National Toxicology Program, 2012; U.S. EPA, 2013). Therefore, it is unclear whether the impact of Pb on CVD mortality risk observed in Menke et al. (2006) is associated with current, past, or cumulative exposures.

It is possible that the relationship predicted by using blood Pb may underestimate the true risk of CVD mortality associated with Pb exposure. This is because using blood Pb will likely result in exposure misclassification, biasing the result toward the null. This occurs because a single blood Pb measurement is highly variable, and, therefore, using the highly variable measurement to predict an outcome adds noise to the model, resulting in an underestimation of the true effect (Personal Communication with Mark Weisskopf, 2013; Rotheman, 1998).

An additional consideration is that of applying the beta estimate derived from a population whose blood Pb levels were measured between 1988 and 1994 to estimate the benefits in the current population. General population blood lead levels fell relatively quickly in the 1980s and 1990s, and continued to fall, but at a slower rate, after the year 2000. The lifetime Pb exposure profile for an adult with a particular blood Pb measurement in 2014 is likely different from that of an individual of the same age with the same blood Pb level in 1992. The individual in 1992 would likely have had higher past Pb exposure. It is unclear how the different past exposure profiles would impact the resulting effect estimate. This is because based on the current data we are unaware what the best model is to relate blood Pb measurements to cardiovascular disease mortality risk (see discussion in Section 5.3).

Additionally, blood Pb levels decreased (from a geometric mean of 2.72 µg/dL in1988-1994 to 1.64 µg/dL in 1999-2002) during the sampling and follow-up period of the NHANES cohort used by of Menke et al. (2006). The implications of this decrease in blood Pb levels throughout the NHANES III time period are unclear. It could be argued that applying the beta estimate based on these higher blood Pb levels to lower blood Pb levels may overestimate the risk. On the contrary, the argument could be made that due to exposure misclassification the beta estimate has been attenuated and is actually underestimating the relationship, assuming the misclassification is random. As the authors point out, "the decrease in blood lead observed at the population level implies that the results of the present study are conservative and that the lead–mortality relationship may be stronger than reported" (Menke et al., 2006, p. 1392-1393).

As discussed in Section 5.2.2, the function used in Menke et al. (2006) was developed using past blood Pb levels (adults in 1988-1994), which are greater than current blood Pb levels. The NHANES III levels were analyzed with a technique that had a limit of detection of 1 µg/dL (CDC, 1996, p. VII-H-12). Therefore, assuming that the linear relationship between log blood Pb and log CVD mortality would hold below the observable range in Menke et al. (2006) introduces uncertainty, as it could be possible that the slope is different at lower blood Pb levels relevant for portions of current and future populations (i.e., blood Pb levels < 1 µg/dL).

The multivariate regression estimates reported in Menke et al. (corresponding to Exhibit 7 and Exhibit 12) could also underestimate the relationship between blood Pb and CVD mortality due to the inclusion of hypertension and kidney function as control variables. The EPA ISA (2013) found associations between Pb exposure and hypertension (causal relationship), as well as reduced kidney function (suggestive of a causal relationship). Controlling for these conditions in the regression means that the coefficient estimate on Pb exposure will not capture any potential indirect effects of Pb exposure in increasing the risk of CVD mortality by the mechanisms of hypertension or impaired kidney function. As can be seen in Exhibit 5, when not controlling for hypertension or kidney function, the hazard ratios were slightly larger compared to controlling for them.

Quantifying these uncertainties is currently not possible. However, if follow-up work from Weisskopf et al. provides a function relating bone Pb to CVD mortality, both the bone and blood Pb functions could be used to estimate benefits to determine how the various models impact the resulting benefits numbers. Additionally, an analysis similar to Menke et al. (2006) is underway by the National Center for Health Statistics to use the more recent NHANES blood Pb data that could help better identify the relationship between blood Pb and CVD mortality at more recent blood Pb levels. If a function is estimated by this analysis, it too could be used to characterize the uncertainty of the relationship between Pb exposure and CVD mortality. These ongoing studies are discussed further in Section 7.

6.1.2 Blood Pb Estimates

The blood Pb levels used in the hypothetical example were based on data from the most recent NHANES analysis (NHANES 2011-2012). Sampling uncertainty exists with these values and can be characterized by using a distribution of blood Pb levels with the proper number of degrees of freedom to account for the complex sampling design used in NHANES 2011-2012. However, blood Pb levels used in benefits estimation for a proposed rule will likely be estimated using exposure modeling. If the exposure model is designed to output a distribution of total blood Pb values at baseline and under regulation, then the resulting distributions can be used to calculate a range of benefits as opposed to just using the mean value. Additional uncertain variables will undoubtedly exist in the exposure modeling. However, given that this report is focused on applying the concentration-response function and not the exposure modeling, we do not further analyze the uncertainty of potential exposure models in this report.

Additionally, blood Pb levels will vary between people (e.g., based on age, gender, socio-demographic group membership). For the hypothetical analysis we characterize some of this variability by deriving benefits estimates for gender/age groups, whose blood Pb levels do vary. However, as with the uncertainty, in order to capture this variability in modeled blood Pb levels, blood Pb estimates could be modeled for various groups of people to determine how the blood Pb concentrations may vary based on an individual's characteristics. Again, given that this report is concentrating on applying the concentration-response function and not the exposure modeling, we do not further analyze the uncertainty of potential exposure models in this report.

6.1.3 Functional Form

As with many concentration-response functions, there is uncertainty about the functional form of the relationship between exposure and response. In considering the relationship between Pb exposure and CVD, Menke et al. (2006) examined several functional forms and concluded that the linear function between log of blood Pb and log of CVD mortality risk best represented the concentration-response

relationship. Additionally, although it is possible for the functional form to vary between population groups, Menke et al. (2006) explored this and found no difference between groups.

6.2 Uncertainty in the Health Impact Function

A health impact function was derived from the concentration-response function. This function allows for a quantification of the number of cases avoided among populations impacted, as illustrated in our hypothetical example. As a reminder this equation is:

$$cases\ \ avoided\ = y_0 * [1 - \left(\frac{x_1}{x_0}\right)^{\beta}] * pop \qquad (3)$$

where y_0 is the baseline CVD mortality per capita rate, x_1 is the blood Pb level with a rule in place, x_0 is the blood Pb level without the rule, and *pop* is the population the rule will impact. In addition to the uncertainty associated with blood Pb measurement and the concentration-response function coefficient estimate (discussed in the previous section), incorporating the baseline mortality rate and the affected population adds additional uncertainty and variability to the benefits estimate. The subsequent sections discuss these additional sources of uncertainty and variability.

6.2.1 Baseline Mortality Rates

The method to characterize uncertainty and variability in the baseline mortality rates for the benefits analysis will be specific to the economic analysis approach and the data sources being used. For example, a specific analysis can either assume that the mortality rate for a given population is the same as the most recent year(s) of data, or it can project what the mortality rate may be in the future year when a rule may be implemented. Uncertainties associated with both approaches need to be examined by the economists developing the analysis in the context of the rule, and then the characterization of these uncertainties can be presented. As for variability, the baseline mortality rate varies by age, gender, socio-demographic group, and location. As with uncertainty, variability should be characterized in the context of the rule. For example, if it is important to understand how benefits vary in different locations across the country, CVD mortality rates may be needed at a smaller geographic resolution compared to the hypothetical example, which used a national estimate. Because the characterization of uncertainty and variability depends on the data sources, approach, and rule-specific needs, exact methods of characterization will not be discussed further in this report.

6.2.2 Population Impacted by the Rule

For any benefits analysis, the population affected by the rule needs to be defined. In the hypothetical example presented, it was assumed 1 million people would be impacted, which is only 0.5% of the total U.S. adult population. The number of people impacted will vary by the policy scenario being considered and will also vary according to many of the same variables that are mentioned when considering uncertainty and variability for the other components of the concentration-response function. Additionally, spatial variation may exist. That is, benefits will be dependent on the area of the United States that is being impacted and the size of the population in that area. The magnitude of the variability of the population impacted could be explored by examining different areas where the rule will be implemented and different population groups that may be impacted. Additionally, uncertainty surrounding the population estimates in certain areas can be characterized by data

provided by the U.S. Census, which can be obtained at the Census tract level. The U.S. Census data provide information on measurement uncertainty in these estimates and could be used to characterize uncertainty surrounding population estimates.

7. Next Steps

We have developed a concentration-response function that allows for the estimation of benefits due to a reduction in risk from CVD mortality as a result of reduced lead exposure in adults. This function is based on Menke et al. (2006), who used one-time blood Pb samples from NHANES III (1988-1994). To understand how this function may change with reduced blood Pb levels (past blood Pb levels are higher than current blood Pb levels), the National Center for Health Statistics is conducting an analysis similar to that conducted by Menke et al. (2006) with more recent NHANES blood Pb samples. When these data become available, we will evaluate them and, if appropriate, use them to update the current function with a new function based on more recent blood Pb levels.

In addition, work is currently underway by Weisskopf et al. to understand the extent to which selection bias may impact the results of their 2009 paper. When these data become available, we will evaluate them to determine if a bone Pb-CVD mortality risk function could be developed. We will also examine the results from the revised blood Pb analysis. This would allow for a deeper understanding of the relationship between current versus cumulative exposure and increased CVD-related mortality risk.

Further, in order to understand additional benefits that may result from reduced Pb exposure, it may be feasible to pursue the development of concentration-response functions for additional endpoints. To select additional endpoints for inclusion in a benefits assessment, we would need to determine if estimates can be provided for morbidity cases (e.g., non-fatal myocardial infarction or increases in blood pressure) that do not result in mortality (e.g., fatal myocardial infarction) and if the interrelationship of the various toxicity endpoints associated with Pb exposure such as cardiovascular and renal endpoints could be separated for the purposes of estimating benefits.

8. References

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Appendix A Overview of Studies Not Selected for Additional Review

This section presents summaries of five studies identified by the EPA ISA and the NTP Monograph that examine the association between Pb exposure and CVD mortality. These are the studies that we did not select for further evaluation as the basis for the development of a concentration-response function.

Cocco et al. (2007)

Cocco et al.'s 2007 study of causes of death among lead smelters in relation to the glucose-6-phosphate dehydrogenase polymorphism (G6PD) assessed the adverse health effects of 933 male Pb smelters in Sardinia, Italy. The study focused on differences in Pb toxicity susceptibility of two cohorts with divergent G6PD polymorphisms. Blood Pb levels were not measured, but the standardized mortality ratios (SMRs) for the Pb smelters' all-cause and CVD deaths were 56 (95% CI: 46, 68) and 37 (95% CI: 25, 55), respectively, when comparing all of the Pb smelters regardless of their G6PD polymorphism with the general population. Given that blood Pb levels were not reported in this study and that the study was in Pb smelters, a group not representative of the adult general population, we did not evaluate the study further to determine if the data presented would be useful in the estimation of a concentration-response function.

Lin et al. (2011)

Lin et al.'s 2011 study, *Association of Blood Lead Levels with Mortality in Patients on Maintenance Hemodialysis,* considered the association between blood Pb levels and mortality in patients on maintenance hemodialysis. The study included 927 patients in Taiwan who had a mean hemodialysis duration of 5.6 ± 2.1 years and were on average 55.7 ± 13.4 years old. The median blood Pb level was 10.4 µg/dL, and all subjects were stratified into three equal groups: low blood Pb level (<8.51 µg/dL), medium blood Pb level (8.51-12.64 µg/dL), and high blood Pb level (>12.64 µg/dL). A Cox multivariate analysis was used to associate baseline blood Pb levels >12.64 µg/dL with higher all-cause mortality (HR = 4.70; 95% CI = 1.92-11.49), cardiovascular-cause mortality (HR = 9.71; 95% CI = 2.11-23.26), and infection-cause mortality (HR = 5.35; 95% CI = 1.38-20.83) in these patients over 18 months of follow-up. We will not use this study in the estimation of a concentration-response function because the association of blood Pb levels and mortality in patients on maintenance hemodialysis is not applicable to the adult general population.

Lustberg & Silbergeld (2002)

Lustberg & Silbergeld's 2002 study of blood Pb levels and mortality evaluated the association of blood Pb levels and mortality in the United States using the 1992 follow-up data for participants in the Second National Health and Nutrition Examination Survey (NHANES II) conducted from 1976 to 1980. The NHANES II survey interviewed a nationally representative sample of 20,322 people, of whom blood Pb levels were available for 4,292 participants. Individuals with blood Pb levels of at least 30 µg/dL were excluded, leaving 4,190 participants. In this group, 19.5% of participants had blood Pb levels <10 µg/dL, 65.3% had blood Pb levels of 10-19 µg/dL, and 15.2% had blood Pb levels of 20-29 µg/dL. The average blood Pb level of the 4,190 participants was 14.0 ± 5.1 µg/dL. Adults with blood Pb levels of 20-29 µg/dL were found to have 46% increased risk for all-cause mortality (risk ratio (RR) = 1.46; 95% CI = 1.14-1.86) and 39% increased risk for circulatory

mortality (RR = 1.39; 95% CI = 1.01-1.91) compared to those with blood Pb levels of <10 µg/dL. Increased all-cause and circulatory mortality was also found in individuals with blood Pb levels of 10-19 µg/dL relative to those with <10 µg/dL. Given that the average blood Pb level of participants was 14.0 ± 5.1 µg/dL, we will not further consider this study in the development of the concentration-response function because the reported average blood Pb level is too high to represent the current average blood Pb levels in the U.S. general population.

Møller & Kristensen (1992)

Møller and Kristensen's 1992 study *Blood Lead as a Cardiovascular Risk Factor* examined the association between blood Pb and blood pressure, total mortality, coronary heart disease and cardiovascular disease mortality. Their cohort included 1,052 men and women from Copenhagen County, Denmark, who had blood Pb measurements taken three times, in 1976, 1981, and 1987 (in 1987 only men were examined). Mean blood Pb concentrations decreased from 13.6 to 8.3 µg/dL from 1976 to 1987 for men, and from 9.6 to 6.8 µg/dL from 1976 to 1981 for women. All participants in the study were followed regarding hospital admissions and deaths for a 14-year follow-up period. The authors found a significant univariate association with total mortality, coronary heart disease, and cardiovascular disease. With regard to coronary heart disease and cardiovascular disease, the association disappeared when the model included confounders. However, the relationship between blood Pb and total mortality remained statistically significant after controlling for confounders. Given that this study did not examine blood Pb as it relates specifically to cardiovascular disease-related mortality, we will not further consider it in the development of the concentration-response function.

Neuberger, Hu, Drake, & Jim (2009)

Neuberger et al.'s 2009 study, *Potential health impacts of heavy-metal exposure at the Tar Creek Superfund site, Ottawa County, Oklahoma,* compared Oklahoma State Department of Health mortality data for residents of five Ottawa County towns located within the boundaries of the Tar Creek Superfund site (i.e., the exposed area) with residents of four Ottawa County towns not within the boundaries of the Tar Creek Superfund site (i.e., the unexposed area). The Tar Creek Superfund site is part of the Tri-State Mining District of Kansas, Missouri, and Oklahoma. In the mid-1980s, parts of the mining district were declared a Superfund site because of the presence of high concentrations of lead, zinc, and cadmium in the mine wastes and tailings, as well as the presence of acid mine water laden with heavy metals emerging from surface and groundwater into the surrounding creeks, especially in Oklahoma. Neuberger et al. compared the occurrence of selected mortality outcomes in Ottawa County (both exposed and unexposed areas) with data for the entire state of Oklahoma. The SMR for death due to hypertension for Ottawa county compared to the state in 1999–2001 was 112.5 (95% CI: 64.3–182.7); the SMR for death due to stroke was 121.6 (95% CI: 119.2–123.9); and the SMR for death due to heart disease was 114.1 (95% CI: 113.1–115.2).

Neuberger et al. also compared the occurrence of selected mortality outcomes for the five exposed Ottawa County cities to the remainder of Ottawa County's population. The SMR for mortality due to hypertension for the five exposed Ottawa County towns compared to data for the rest of the county in 1999–2001 was 144.9 (95% CI: 39.5–370.9); the SMR for death due to stroke was 69.9 (95% CI: 37.2–119.6); and the SMR for heart disease-caused mortality was 90.9 (95% CI: 71.0–114.7). The Neuberger et al. (2009) study also discusses which Oklahoma cities had the highest percentages of elevated blood Pb levels for children under 6 years old in 1996–2000. Given that exposure in this

study is determined by residence and not blood Pb levels, and blood Pb levels are not reported for adults, we cannot use this study to estimate the concentration-response function.

Appendix B Discussion of Blood Pb, Bone Pb, and Their Interrelationship

Once Pb enters the body (through either inhalation or ingestion), it enters the blood stream and has a clearance half-life of approximately 30 days. Clearance of Pb from blood occurs through "the distribution into soft tissues and bone as well as excretion, primarily through kidney filtration and elimination in urine" (Hu, Shih, Rothenberg, & Schwartz, 2007, p. 456). The loss of bone Pb occurs slowly through bone resorption,[10] the dominant transfer process for bone Pb, and by diffusion (U.S. EPA, 2013). Half-time of Pb in bone is dependent on age, intensity of exposure, and bone type. EPA states that for cortical bone, the half-time of lead at birth is 0.23 years, 1.2 years at 5 years of age, 3.7 years at 15 years of age, and 23 years in adults; for trabecular bone, the half-time of lead at birth is 0.23 years, 1.0 years at 5 years of age, 2.0 years at 15 years of age, and 3.9 years in adults (U.S. EPA, 2013).

Although Pb can circulate throughout the body and can be found in all organs and tissues, blood is the most readily available biomarker for Pb exposure. It is reflective of both recent exposures (<30 days) from exogenous sources and past exposures (years to decades) that had been stored in tissues (e.g., bone) and released endogenously (National Toxicology Program, 2012; U.S. EPA, 2013). As stated previously, the half-life of blood Pb is approximately 30 days, but Hu et al. (2007) point out that this half-life is:

> "a reflection of the 120-day lifespan of erythrocytes and only applies in practice if the total exposure is short (e.g., <30 days). If lead exposure is long-term (i.e., with a duration of years), upon cessation the kinetics of clearance of lead from blood is considerably more complicated, with an initial rapid decline in levels reflecting partial clearance from blood and other soft tissues followed by a much slower clearance, reflecting the replenishment of soft tissue polls of lead with lead from long-lived deposits in bone" (p. 457).

Further, when we discuss blood Pb, we are referring to Pb in whole blood. However, plasma Pb, which is less than 1% (U.S. EPA, 2013) to less than 5% (National Toxicology Program, 2012) of whole blood Pb, is the portion of blood Pb that enters specific tissues and is what is of interest when understanding the toxic impacts of Pb. Unfortunately, plasma Pb is difficult to measure and is subsequently not readily available or used in epidemiological studies. This can result in exposure misclassification given that the ratio of whole blood Pb to plasma blood Pb is not well characterized, and therefore it is unclear how much Pb reaches a target organ. It is also important to note that different techniques for quantifying Pb in whole blood or plasma measurements can limit comparability across studies, especially when methods with high levels of detection are used (National Toxicology Program, 2012).

Blood Pb is only representative of approximately 1% of an individual's body burden, and therefore additional exposure misclassification may be introduced especially with studies that only provide one blood Pb measurement at one point in time (U.S. EPA, 2013). That is, simply because an individual has a high blood Pb level at one time, this does not imply that he/she has had a lifetime of high Pb exposures.

[10] Bone resorption is the breakdown of bone tissue in order to release calcium to the blood.

However, methods have been developed to estimate cumulative Pb exposure or indicators of cumulative Pb exposure based on blood Pb measurements. One such method is time-integrated blood Pb, often referred to as the cumulative blood lead index (CBLI),[11] which uses multiple blood Pb measurements and the trapezoidal rule[12] to estimate an acceptable cumulative Pb dose surrogate (Hu et al., 2007). Another such technique, developed by Park et al. (Park et al., 2009), uses blood Pb levels and other standard covariates (e.g., blood Pb, age, education, occupation, cumulative cigarette smoking, and smoking status) to predict bone Pb levels. This model used a subset of data from the Normative Aging Study and found that blood Pb accounted for approximately 9% (tibia) to 13% (patella) of the variability in bone Pb levels. Inclusion of age in the regression model accounted for an additional 7-10% of the variability in bone Pb (Park et al., 2009).

Bone Pb, a more recently developed biomarker of Pb exposure, can be interpreted as a person's cumulative exposure. This is because of the long half-life of Pb in bone that results in bone lead representing 90% of an adult's body burden (U.S. EPA, 2013). There are two types of bone, cortical and trabecular, both of which can accumulate Pb. Trabecular bone is a spongier, more porous bone, such as the interior of the patella (~20% of adult bone), and cortical bone is a denser bone such as the shaft of the tibia (~80% of adult bone) (U.S. EPA, 2013; Wittmers Jr., Aufderheide, Wallgren, Rapp, & Alich, 1988). The trabecular bone, given its shorter half-life of approximately 4 years, is more representative of recent exposure. Additionally, trabecular bone may provide more of the Pb in circulation "due to its larger surface area allowing for more Pb to bind via ion exchange mechanisms and more rapid turnover, making it more sensitive to changing patterns of exposure" (U.S. EPA, 2013, p. 3-68). Cortical bone, on the other hand, has an approximate half-life of more than 20 years and is more representative of cumulative exposure (U.S. EPA, 2013).

According to EPA, uptake of Pb to bone depends on calcification rates (the rate at which the bone is being formed or remodeled[13]). In infancy and childhood, calcification is most active in trabecular bone. Additionally, given the high bone formation rate in early childhood, there is a rapid uptake of Pb into mineralizing bone. However, there is also a high bone resorption rate, and therefore "much of the Pb acquired early in life is not permanently fixed in the bone" (U.S. EPA, 2013, p. 1-12). In adulthood calcification occurs mainly at sites of remodeling in cortical and trabecular bones (U.S. EPA, 2013). Further, during times of physiologic stress such as pregnancy, lactation, menopause, extended bed rest, hyperparathyroidism, or severe weight loss, mobilization of Pb from bone into blood increases. Interestingly, Nie et al. (2009) found that although bone lead was significantly associated with blood Pb in a population of elderly men (from the Normative Aging Study), age and bone resorption rates did not significantly modify this association. They hypothesize that lead distribution in bone is uneven and that lead is stored in less active bone sites for elderly people. Further research on this is needed to confirm this finding. The EPA ISA (U.S. EPA, 2013) states that

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[11] The process for deriving the CBLI can be found in Appendix A of Hu et al. (2007).

[12] A technique for approximating the area under a graph of a function.

[13] Bone remodeling is the process of breaking down of bone tissue in order to release calcium to the blood (referred to as resorption) and forming of new bone. It occurs throughout the life of an individual.

based on limited studies, bone Pb stores can contribute as much as 40–70% to blood Pb. However, Hu et al. (2007) state that the variation in blood Pb is mainly due to changes in external exposure.

Bone Pb is most often measured with a k-xray fluorescence (K-XRF) machine. However, the most commonly used K-XRF machines have a wide measurement error (National Toxicology Program, 2012; U.S. EPA, 2013). As with blood Pb, comparing studies that uses different calibration techniques may limit one's ability to compare the results between studies. Further, some methods may be impacted by the thickness of skin over the measurement site, which may be a concern for studies that include obese people (National Toxicology Program, 2012). Additionally, measurements from K-XRF are often given in terms of bone density, which can introduce uncertainty in regard to the Pb measurements and may have implications for studies in individuals with low bone density (e.g., older women) (U.S. EPA, 2013).

Appendix C Absolute Change

Exhibit C-1. Benefits from Absolute Change in Unstratified Blood Pb Cutoff

Age Group	Gender	0.05 µg/dL increase						1.0 µg/dL increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.07	0.16	0.25	$0.60	$1.40	$2.10	0.86	1.86	2.72	$7.30	$15.70	$22.90
	F	0.06	0.13	0.20	$0.50	$1.10	$1.70	0.57	1.20	1.72	$4.80	$10.20	$14.50
30-39	M	0.21	0.48	0.74	$1.70	$4.00	$6.30	2.54	5.51	8.08	$21.40	$46.50	$68.10
	F	0.16	0.38	0.59	$1.40	$3.20	$5.00	1.73	3.67	5.26	$14.60	$31.00	$44.40
40-49	M	0.62	1.44	2.25	$5.20	$12.10	$19.00	8.17	17.92	26.52	$68.90	$151.10	$223.50
	F	0.39	0.90	1.41	$3.30	$7.60	$11.80	4.72	10.22	14.94	$39.80	$86.20	$125.90
50-59	M	1.21	2.81	4.40	$10.20	$23.70	$37.10	17.16	38.02	56.80	$144.60	$320.50	$478.80
	F	0.68	1.59	2.48	$5.80	$13.40	$20.90	9.10	19.97	29.56	$76.70	$168.30	$249.20
60-69	M	1.61	3.73	5.85	$13.50	$31.50	$49.30	22.95	51.02	76.47	$193.40	$430.10	$644.70
	F	1.14	2.66	4.16	$9.60	$22.40	$35.10	15.43	33.93	50.30	$130.10	$286.00	$424.00
70-80	M	2.09	4.86	7.62	$17.60	$41.00	$64.20	31.01	69.18	104.00	$261.50	$583.20	$876.70
	F	2.26	5.25	8.22	$19.10	$44.30	$69.30	30.72	67.83	100.96	$259.00	$571.80	$851.10
Total (20-80 years)	**M**	5.80	13.49	21.12	$48.90	$113.70	$178.00	82.68	183.53	274.59	$697.00	$1,547.10	$2,314.80
	F	4.69	10.90	17.06	$39.60	$91.90	$143.80	62.27	136.82	202.73	$525.00	$1,153.40	$1,709.00
	Both	10.50	24.39	38.18	$88.50	$205.60	$321.80	144.96	320.35	477.32	$1,222.00	$2,700.50	$4,023.80

Exhibit C-2. Benefits from Absolute Change for a Blood Pb Cutoff of Above 1.0 µg/dL

Age Group	Gender	0.05 µg/dL increase						1.0 µg/dL increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.01	0.03	0.05	$0.10	$0.30	$0.40	0.20	0.44	0.66	$1.70	$3.70	$5.60
	F	0.00	0.01	0.01	$0.00	$0.00	$0.10	0.03	0.07	0.11	$0.30	$0.60	$0.90
30-39	M	0.06	0.13	0.20	$0.50	$1.10	$1.70	0.82	1.81	2.71	$6.90	$15.30	$22.90
	F	0.01	0.02	0.04	$0.10	$0.20	$0.30	0.15	0.32	0.48	$1.20	$2.70	$4.00
40-49	M	0.24	0.56	0.87	$2.00	$4.70	$7.40	3.61	8.05	12.10	$30.40	$67.90	$102.00
	F	0.08	0.19	0.30	$0.70	$1.60	$2.50	1.23	2.73	4.09	$10.40	$23.00	$34.50
50-59	M	0.71	1.65	2.59	$6.00	$13.90	$21.80	10.83	24.20	36.46	$91.30	$204.00	$307.40
	F	0.30	0.71	1.11	$2.60	$5.90	$9.30	4.53	10.08	15.11	$38.20	$85.00	$127.40
60-69	M	1.09	2.53	3.97	$9.20	$21.30	$33.40	16.68	37.35	56.36	$140.60	$314.90	$475.10
	F	0.54	1.26	1.97	$4.60	$10.60	$16.60	8.13	18.09	27.15	$68.50	$152.50	$228.90
70-80	M	1.61	3.74	5.86	$13.50	$31.50	$49.40	24.92	55.83	84.29	$210.10	$470.70	$710.60
	F	1.15	2.68	4.21	$9.70	$22.60	$35.40	17.59	39.29	59.15	$148.30	$331.20	$498.60
Total (20-80 years)	**M**	3.71	8.64	13.54	$31.30	$72.80	$114.10	57.05	127.69	192.59	$481.00	$1,076.40	$1,623.50
	F	2.09	4.87	7.63	$17.60	$41.00	$64.30	31.65	70.59	106.09	$266.80	$595.10	$894.30
	Both	5.81	13.51	21.17	$48.90	$113.90	$178.40	88.71	198.28	298.67	$747.80	$1,671.50	$2,517.80

Exhibit C-3. Benefits from Absolute Change for a Blood Pb Cutoff of Above 1.46 µg/dL

Age Group	Gender	0.05 µg/dL increase						1.0 µg/dL increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.01	0.01	0.02	$0.00	$0.10	$0.10	0.08	0.17	0.26	$0.70	$1.50	$2.20
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.03	0.04	$0.10	$0.20	$0.30
30-39	M	0.02	0.05	0.08	$0.20	$0.40	$0.70	0.34	0.77	1.16	$2.90	$6.50	$9.80
	F	0.00	0.01	0.01	$0.00	$0.10	$0.10	0.04	0.09	0.14	$0.30	$0.80	$1.20
40-49	M	0.11	0.26	0.41	$0.90	$2.20	$3.40	1.78	4.01	6.08	$15.00	$33.80	$51.30
	F	0.03	0.06	0.09	$0.20	$0.50	$0.80	0.40	0.91	1.37	$3.40	$7.60	$11.60
50-59	M	0.39	0.91	1.43	$3.30	$7.70	$12.00	6.26	14.09	21.38	$52.80	$118.80	$180.20
	F	0.13	0.31	0.48	$1.10	$2.60	$4.00	2.07	4.65	7.04	$17.50	$39.20	$59.30
60-69	M	0.58	1.36	2.13	$4.90	$11.40	$17.90	9.45	21.32	32.41	$79.70	$179.80	$273.20
	F	0.25	0.57	0.90	$2.10	$4.80	$7.60	3.90	8.74	13.23	$32.80	$73.70	$111.50
70-80	M	1.02	2.38	3.73	$8.60	$20.00	$31.40	16.50	37.17	56.42	$139.10	$313.40	$475.60
	F	0.63	1.46	2.29	$5.30	$12.30	$19.30	10.05	22.60	34.26	$84.70	$190.50	$288.80
Total (20-80 years)	**M**	2.13	4.96	7.79	$18.00	$41.90	$65.60	34.42	77.54	117.72	$290.10	$653.70	$992.40
	F	1.03	2.40	3.76	$8.70	$20.20	$31.70	16.47	37.02	56.07	$138.80	$312.10	$472.70
	Both	3.16	7.37	11.55	$26.70	$62.10	$97.40	50.89	114.57	173.79	$429.00	$965.80	$1,465.10

Exhibit C-4. Benefits from Absolute Change for a Blood Pb Cutoff of Above 2.0 µg/dL

Age Group	Gender	0.05 µg/dL increase						1.0 µg/dL increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.00	0.00	0.01	$0.00	$0.00	$0.10	0.03	0.07	0.11	$0.30	$0.60	$0.90
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.00	0.01	0.01	$0.00	$0.10	$0.10
30-39	M	0.01	0.02	0.03	$0.10	$0.10	$0.20	0.12	0.28	0.42	$1.00	$2.30	$3.60
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.03	0.05	$0.10	$0.30	$0.40
40-49	M	0.04	0.09	0.15	$0.30	$0.80	$1.20	0.68	1.54	2.35	$5.70	$12.90	$19.80
	F	0.01	0.02	0.04	$0.10	$0.20	$0.30	0.17	0.39	0.59	$1.40	$3.20	$5.00
50-59	M	0.17	0.40	0.62	$1.40	$3.30	$5.30	2.86	6.49	9.93	$24.10	$54.70	$83.70
	F	0.05	0.11	0.17	$0.40	$0.90	$1.50	0.78	1.77	2.70	$6.60	$14.90	$22.70
60-69	M	0.31	0.72	1.13	$2.60	$6.10	$9.50	5.23	11.88	18.16	$44.10	$100.10	$153.10
	F	0.07	0.16	0.25	$0.60	$1.30	$2.10	1.14	2.58	3.95	$9.60	$21.80	$33.30
70-80	M	0.51	1.19	1.86	$4.30	$10.00	$15.70	8.59	19.46	29.70	$72.40	$164.00	$250.40
	F	0.27	0.64	1.00	$2.30	$5.40	$8.40	4.59	10.41	15.89	$38.70	$87.70	$133.90
Total (20-80 years)	**M**	1.04	2.42	3.80	$8.80	$20.40	$32.00	17.51	39.71	60.66	$147.60	$334.70	$511.40
	F	0.40	0.93	1.46	$3.40	$7.80	$12.30	6.71	15.19	23.18	$56.50	$128.00	$195.40
	Both	1.44	3.35	5.26	$12.10	$28.30	$44.30	24.22	54.90	83.84	$204.10	$462.80	$706.80

Exhibit C-5. Benefits from Absolute Change for a Blood Pb Cutoff of Above 3.62 µg/dL

Age Group	Gender	0.05 µg/dL increase						1.0 µg/dL increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.02	0.03	$0.10	$0.20	$0.20
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.00	0.00	0.00	$0.00	$0.00	$0.00
30-39	M	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.01	0.02	$0.10	$0.10	$0.20
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.00	0.00	0.01	$0.00	$0.00	$0.10
40-49	M	0.01	0.01	0.02	$0.00	$0.10	$0.20	0.10	0.22	0.35	$0.80	$1.90	$2.90
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.02	0.05	0.08	$0.20	$0.40	$0.60
50-59	M	0.02	0.05	0.07	$0.20	$0.40	$0.60	0.36	0.83	1.28	$3.00	$7.00	$10.80
	F	0.00	0.01	0.02	$0.00	$0.10	$0.10	0.07	0.17	0.26	$0.60	$1.40	$2.20
60-69	M	0.06	0.14	0.22	$0.50	$1.20	$1.90	1.08	2.47	3.81	$9.10	$20.80	$32.10
	F	0.01	0.03	0.04	$0.10	$0.20	$0.40	0.21	0.47	0.73	$1.70	$4.00	$6.10
70-80	M	0.08	0.18	0.28	$0.60	$1.50	$2.40	1.38	3.15	4.85	$11.60	$26.50	$40.90
	F	0.04	0.10	0.15	$0.30	$0.80	$1.30	0.74	1.68	2.60	$6.20	$14.20	$21.90
Total (20-80 years)	**M**	0.16	0.38	0.60	$1.40	$3.20	$5.00	2.92	6.70	10.34	$24.60	$56.40	$87.10
	F	0.06	0.14	0.21	$0.50	$1.10	$1.80	1.04	2.37	3.66	$8.70	$20.00	$30.90
	Both	0.22	0.51	0.81	$1.90	$4.30	$6.80	3.96	9.07	14.00	$33.40	$76.50	$118.00

Appendix D Percentage Change

Exhibit D-1. Benefits from Percentage Change for an Unstratified Blood Pb Cutoff

Age Group	Gender	5% increase						50% increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.06	0.13	0.21	$0.50	$1.10	$1.70	0.46	1.03	1.56	$3.90	$8.70	$13.20
	F	0.03	0.07	0.10	$0.20	$0.60	$0.90	0.23	0.52	0.78	$1.90	$4.30	$6.60
30-39	M	0.18	0.41	0.64	$1.50	$3.50	$5.40	1.44	3.22	4.86	$12.10	$27.10	$41.00
	F	0.09	0.21	0.33	$0.80	$1.80	$2.80	0.74	1.65	2.49	$6.20	$13.90	$21.00
40-49	M	0.66	1.52	2.38	$5.50	$12.80	$20.10	5.31	11.91	18.00	$44.80	$100.40	$151.70
	F	0.32	0.73	1.14	$2.70	$6.20	$9.60	2.55	5.72	8.64	$21.50	$48.20	$72.80
50-59	M	1.65	3.83	5.99	$13.90	$32.30	$50.50	13.34	29.91	45.18	$112.40	$252.10	$380.90
	F	0.74	1.71	2.68	$6.20	$14.40	$22.60	5.97	13.38	20.21	$50.30	$112.80	$170.40
60-69	M	2.35	5.46	8.55	$19.80	$46.10	$72.00	19.04	42.70	64.51	$160.50	$360.00	$543.80
	F	1.29	2.99	4.67	$10.80	$25.20	$39.40	10.41	23.35	35.28	$87.80	$196.80	$297.40
70-80	M	3.40	7.90	12.35	$28.70	$66.60	$104.10	27.51	61.69	93.21	$231.90	$520.10	$785.70
	F	2.75	6.39	9.99	$23.20	$53.80	$84.20	22.26	49.91	75.40	$187.60	$420.70	$635.60
Total (20-80 years)	**M**	8.29	19.26	30.11	$69.90	$162.30	$253.80	67.11	150.46	227.32	$565.70	$1,268.40	$1,916.30
	F	5.21	12.10	18.92	$43.90	$102.00	$159.50	42.15	94.51	142.79	$355.30	$796.70	$1,203.80
	Both	13.50	31.35	49.03	$113.80	$264.30	$413.30	109.26	244.97	370.12	$921.00	$2,065.10	$3,120.10

Exhibit D-2. Benefits from Percentage Change for a Blood Pb Cutoff of above 1.0 µg/dL

Age Group	Gender	5% increase						50% increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.02	0.05	0.08	$0.20	$0.40	$0.60	0.17	0.38	0.57	$1.40	$3.20	$4.80
	F	0.00	0.01	0.01	$0.00	$0.10	$0.10	0.03	0.06	0.09	$0.20	$0.50	$0.80
30-39	M	0.08	0.19	0.30	$0.70	$1.60	$2.50	0.67	1.50	2.26	$5.60	$12.60	$19.10
	F	0.01	0.03	0.05	$0.10	$0.30	$0.40	0.12	0.26	0.39	$1.00	$2.20	$3.30
40-49	M	0.39	0.91	1.43	$3.30	$7.70	$12.00	3.18	7.12	10.76	$26.80	$60.00	$90.70
	F	0.12	0.29	0.45	$1.00	$2.40	$3.80	1.00	2.25	3.40	$8.50	$18.90	$28.60
50-59	M	1.25	2.90	4.53	$10.50	$24.40	$38.20	10.10	22.64	34.20	$85.10	$190.80	$288.30
	F	0.47	1.09	1.70	$3.90	$9.10	$14.30	3.78	8.48	12.81	$31.90	$71.50	$108.00
60-69	M	1.99	4.62	7.23	$16.80	$39.00	$60.90	16.11	36.12	54.57	$135.80	$304.50	$460.10
	F	0.85	1.98	3.10	$7.20	$16.70	$26.20	6.91	15.50	23.42	$58.30	$130.70	$197.40
70-80	M	3.03	7.03	10.99	$25.50	$59.20	$92.60	24.49	54.90	82.95	$206.40	$462.80	$699.30
	F	1.99	4.63	7.23	$16.80	$39.00	$61.00	16.12	36.14	54.61	$135.90	$304.70	$460.30
Total (20-80 years)	**M**	6.76	15.70	24.55	$57.00	$132.30	$206.90	54.70	122.65	185.31	$461.20	$1,034.00	$1,562.20
	F	3.46	8.02	12.55	$29.10	$67.60	$105.80	27.96	62.69	94.71	$235.70	$528.40	$798.40
	Both	10.22	23.72	37.09	$86.10	$200.00	$312.70	82.66	185.34	280.02	$696.80	$1,562.40	$2,360.60

Exhibit D-3. Benefits from Percentage Change for a Blood Pb Cutoff of above 1.46 µg/dL

Age Group	Gender	5% increase						50% increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.01	0.03	0.04	$0.10	$0.20	$0.30	0.09	0.20	0.30	$0.70	$1.70	$2.50
	F	0.00	0.00	0.01	$0.00	$0.00	$0.00	0.01	0.03	0.04	$0.10	$0.20	$0.30
30-39	M	0.04	0.10	0.16	$0.40	$0.80	$1.30	0.35	0.78	1.18	$2.90	$6.60	$10.00
	F	0.01	0.01	0.02	$0.00	$0.10	$0.20	0.05	0.10	0.15	$0.40	$0.90	$1.30
40-49	M	0.24	0.55	0.87	$2.00	$4.70	$7.30	1.93	4.32	6.53	$16.30	$36.50	$55.10
	F	0.05	0.13	0.20	$0.50	$1.10	$1.70	0.44	0.98	1.49	$3.70	$8.30	$12.50
50-59	M	0.86	2.01	3.14	$7.30	$16.90	$26.50	6.99	15.68	23.69	$58.90	$132.20	$199.70
	F	0.26	0.61	0.95	$2.20	$5.10	$8.00	2.11	4.73	7.14	$17.80	$39.90	$60.20
60-69	M	1.38	3.21	5.01	$11.60	$27.00	$42.30	11.17	25.05	37.85	$94.20	$211.20	$319.00
	F	0.50	1.15	1.80	$4.20	$9.70	$15.20	4.02	9.01	13.61	$33.90	$75.90	$114.70
70-80	M	2.31	5.36	8.39	$19.50	$45.20	$70.70	18.69	41.91	63.32	$157.60	$353.30	$533.80
	F	1.36	3.15	4.92	$11.40	$26.50	$41.50	10.97	24.60	37.17	$92.50	$207.40	$313.40
Total (20-80 years)	**M**	4.85	11.25	17.60	$40.90	$94.90	$148.40	39.22	87.94	132.86	$330.60	$741.30	$1,120.00
	F	2.17	5.05	7.90	$18.30	$42.60	$66.60	17.60	39.45	59.61	$148.30	$332.60	$502.50
	Both	7.02	16.30	25.49	$59.20	$137.40	$214.90	56.82	127.39	192.47	$479.00	$1,073.90	$1,622.50

Exhibit D-4. Benefits from Percentage Change for a Blood Pb Cutoff of above 2.0 µg/dL

Age Group	Gender	5% increase						50% increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.01	0.01	0.02	$0.00	$0.10	$0.20	0.05	0.10	0.16	$0.40	$0.90	$1.30
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.01	0.02	$0.00	$0.10	$0.10
30-39	M	0.02	0.05	0.07	$0.20	$0.40	$0.60	0.16	0.35	0.53	$1.30	$3.00	$4.50
	F	0.00	0.01	0.01	$0.00	$0.10	$0.10	0.02	0.05	0.08	$0.20	$0.40	$0.60
40-49	M	0.12	0.28	0.43	$1.00	$2.30	$3.60	0.96	2.15	3.25	$8.10	$18.20	$27.40
	F	0.03	0.07	0.11	$0.20	$0.60	$0.90	0.24	0.53	0.80	$2.00	$4.40	$6.70
50-59	M	0.50	1.16	1.82	$4.20	$9.80	$15.30	4.05	9.09	13.73	$34.20	$76.60	$115.80
	F	0.12	0.28	0.44	$1.00	$2.40	$3.70	0.97	2.18	3.30	$8.20	$18.40	$27.80
60-69	M	0.93	2.15	3.36	$7.80	$18.10	$28.30	7.49	16.79	25.36	$63.10	$141.50	$213.80
	F	0.20	0.45	0.71	$1.60	$3.80	$6.00	1.58	3.54	5.35	$13.30	$29.90	$45.10
70-80	M	1.44	3.35	5.24	$12.20	$28.30	$44.20	11.69	26.20	39.59	$98.50	$220.90	$333.70
	F	0.77	1.78	2.79	$6.50	$15.00	$23.50	6.21	13.93	21.04	$52.40	$117.40	$177.40
Total (20-80 years)	**M**	3.01	7.00	10.94	$25.40	$59.00	$92.30	24.39	54.69	82.62	$205.60	$461.00	$696.50
	F	1.12	2.59	4.05	$9.40	$21.80	$34.10	9.03	20.24	30.57	$76.10	$170.60	$257.70
	Both	4.13	9.59	14.99	$34.80	$80.80	$126.40	33.42	74.92	113.20	$281.70	$631.60	$954.30

Exhibit D-5. Benefits from Percent Change for a Blood Pb Cutoff of Above 3.62 µg/dL

Age Group	Gender	5% increase						50% increase					
		Annual Cases Avoided			Annual Benefits (2012$ million)			Annual Cases Avoided			Annual Benefits (2012$ million)		
		L	C	U	L	C	U	L	C	U	L	C	U
20-29	M	0.00	0.01	0.01	$0.00	$0.00	$0.10	0.02	0.04	0.06	$0.20	$0.30	$0.50
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.00	0.00	0.00	$0.00	$0.00	$0.00
30-39	M	0.00	0.01	0.01	$0.00	$0.00	$0.10	0.02	0.04	0.06	$0.10	$0.30	$0.50
	F	0.00	0.00	0.00	$0.00	$0.00	$0.00	0.01	0.01	0.02	$0.10	$0.10	$0.20
40-49	M	0.03	0.08	0.12	$0.30	$0.60	$1.00	0.27	0.60	0.90	$2.20	$5.00	$7.60
	F	0.01	0.02	0.03	$0.10	$0.10	$0.20	0.06	0.14	0.21	$0.50	$1.10	$1.70
50-59	M	0.13	0.29	0.46	$1.10	$2.50	$3.90	1.03	2.30	3.48	$8.70	$19.40	$29.30
	F	0.02	0.05	0.07	$0.20	$0.40	$0.60	0.16	0.37	0.55	$1.40	$3.10	$4.70
60-69	M	0.30	0.69	1.08	$2.50	$5.80	$9.10	2.41	5.41	8.17	$20.30	$45.60	$68.80
	F	0.06	0.13	0.20	$0.50	$1.10	$1.70	0.44	0.99	1.50	$3.70	$8.40	$12.60
70-80	M	0.34	0.80	1.25	$2.90	$6.70	$10.50	2.78	6.23	9.41	$23.40	$52.50	$79.40
	F	0.19	0.44	0.69	$1.60	$3.70	$5.80	1.53	3.43	5.18	$12.90	$28.90	$43.70
Total (20-80 years)	**M**	0.81	1.87	2.92	$6.80	$15.80	$24.60	6.52	14.61	22.08	$54.90	$123.20	$186.10
	F	0.27	0.63	0.99	$2.30	$5.30	$8.30	2.20	4.94	7.47	$18.60	$41.70	$62.90
	Both	1.08	2.50	3.91	$9.10	$21.10	$33.00	8.72	19.55	29.54	$73.50	$164.80	$249.00