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

Updated Draft April 5, 2019

Prepared for:
National Center for
Environmental Economics
Office of Policy
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Submitted by:
Meghan Lynch, Lauren Brown, Andrea Chiger and Ryan Klein
Abt Associates Inc.
6130 Executive Boulevard
Rockville, MD 20852

Table of Contents

1. Introduction

Lead (Pb) is a well-known toxicant that has been associated with a range of adverse health effects, including impairments to the neurological, cardiovascular, and immunological systems. However, in benefit-cost analyses (BCAs) for regulations that aim to decrease Pb exposures, EPA typically has focused on monetizing avoided IQ loss in children. Additional adverse health effects are considered qualitatively, despite strong epidemiological evidence that demonstrates an association between Pb exposure and a multitude of additional endpoints. Because these additional adverse health outcomes are not quantified, the economic benefits of reduced Pb exposures are likely underestimated in EPA BCAs.

EPA has directed Abt Associates to produce a series of reports to develop quantitative approaches to include additional health endpoints in economic benefits analyses for regulations that reduce Pb exposure. These endpoints are: cardiovascular disease related mortality (CVD mortality) and morbidity in Pb exposed adults, reduced birth weight in infants after prenatal Pb exposure, and attention deficit hyperactivity disorder (ADHD) in Pb exposed children. Selection of these endpoints for possible inclusion in benefits analysis does not preclude future consideration of other adverse health outcomes associated with Pb. This report specifically addresses the relationship between Pb exposure and CVD mortality. A previous version of this report was reviewed in 2015 as part of the external peer review of EPA's Approach for Estimating Exposures and Incremental Health Effects for Pb due to Renovation, Repair and Painting Activities in Public and Commercial Buildings (U.S. EPA, 2015). However, since that time, additional studies have been published. Therefore, a new peer review of this report is necessary which reflects the most up to date information based on the inclusion of these additional studies.

In this section we provide context for the report by describing the general approach for conducting benefits analysis (Section 1.1). Additionally, we provide an outline for the remainder of the report (Section 1.2).

1.1   Approach to Informing Benefits Analyses

BCA is used to compare the favorable effects of a policy (i.e., the benefits) with the potential costs of the same policy (U.S. EPA, 2014). Benefits and costs of a policy are typically expressed in monetary terms, facilitating the aggregation and comparison of the health and ecological benefits to the costs of implementation by using common units. Benefits that are not quantified or monetized in BCA are often viewed as being implicitly assigned a value of zero. Therefore, it is important to be as comprehensive as possible when assessing the benefits and costs of a policy change, with a goal of fully quantifying both. Efforts to quantify health benefits should consider both the types of health effects and the affected populations. Federal environmental regulations often result in changes in exposure for the entire U.S. population, including sensitive populations.

Incorporating health effects in benefits analysis is a multi-step process that involves four broad components: (1) estimating or projecting changes in emissions or stressors as a result of policy decisions compared to a baseline, pre-policy scenario; (2) quantifying the associated change in human exposures to those changes in stressors; (3) quantifying the changes in health risks caused by the change in exposure from a pre-policy scenario; and (4) valuing the changes in health risks in monetary terms (Exhibit 1). This report focuses on the third component—quantifying changes in health risks caused by reductions in Pb exposure. These changes are estimated by identifying appropriate dose-response or concentration-response functions from the scientific literature and then applying these functions to the exposed population affected by a regulation (typically the entire U.S. population).

Exhibit 1.   Summary of the Steps Involved in Quantifying the Health Benefits for Regulations
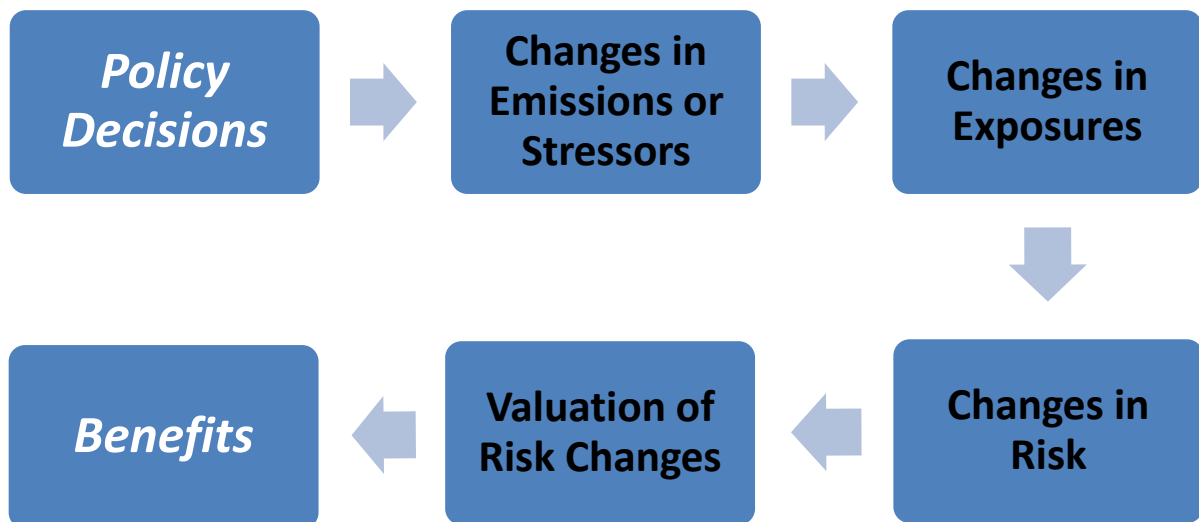
The following major factors drove decisions about which health endpoints and studies were considered in this series of reports:

1. Health endpoints used in quantitative benefits analysis must be amenable to monetization. Endpoints such as changes in mortality risk, IQ, and incidence of specific diseases or health conditions that result in medical or other quantifiable costs can all be valued using standard economic approaches. However, other health indicators or measures are less amenable to benefits analysis even though they may be relevant for clinical use or diagnosis. In some cases, more than one dose-response function or probability functions may be necessary in order to monetize endpoints. For example, a dose-response function may be available linking contaminant exposure to changes in bone mineralization, but a second function may need to be used to link these changes in bone mineralization to increased risk of fracture, an endpoint which may be monetized. In other cases it may be difficult to quantify the link to a monetizable endpoint from the

measure(s) available in the literature. For example, epidemiological studies of behavioral effects frequently test children's performance on a Continuous Performance Task (CPT). In a CPT, the child is instructed to respond (by pressing a space bar or clicking a mouse) only when certain images (such as an "X") appear on a computer monitor. This kind of test can identify deficits in various types of mental function, such as alertness and other aspects of attention that may be associated with Pb exposure. However, there is not an established framework for monetizing or establishing a value for avoiding these attention decrements, nor can these tests by themselves be used to assess the likelihood of an ADHD diagnosis. Other testing measures present similar challenges. Since there are multiple endpoints associated with exposure to Pb, we first focus on specific health outcomes that can be directly linked to welfare or monetary measures.

2. Quantifying benefits in the general population often requires a different decision making process than the process for setting a health protective standard intended to also protect the most sensitive members of the population.

    a. Measures of exposure and risk used in benefits analysis do not aim to over- or under-state expected risk or changes in health outcomes in the exposed population of interest. Judgments and assumptions are often required to estimate individual or population risks. For rulemakings that affect the entire population, study findings should be able to support development of risk estimates applicable to the general population or some substantial proportion thereof.

    b. Studies or results from the epidemiological literature that focus on outcomes near the tails of the risk distribution for highly sensitive endpoints or subpopulations could lead to biased or uncertain benefits estimates if extrapolated to the general population. Therefore, if available and appropriate, it is preferable to use studies of the general population and exposure levels most relevant to policy rather than those conducted on populations with special health considerations or those focusing on the most highly exposed individuals (e.g., occupationally exposed workers).

3. Benefits analysis requires quantified dose-response relationships between exposures and health outcomes. Often, if the data is available, it is most useful if health outcomes are measured as continuous rather than binary outcomes (e.g., birth weight rather than a binary indicator for above or below the low birth weight threshold). Continuous health outcome measures allow analysts to quantify incremental changes in risk for the entire exposed population, not just the subset of the population that would cross a given threshold in response to a particular policy change.

4. The quantified dose-response relationships between exposure and health outcomes should be specific to associations with enough evidence to be reasonably associated with the exposure of interest. In the case of Pb, formal weight-of-evidence

characterizations are available, and we focus on those endpoints judged to be in the top three tiers of these evaluations (see Section 2.1).

1.2   Outline of Report

The purpose of this report is to summarize our approach and results of developing a quantitative approach for evaluating benefits of reduced Pb exposure and subsequent reduced risk of CVD mortality. Previously, the EPA conducted a weight-of-evidence assessment in the *Integrated Science Assessment for Lead* (hereafter referred to as the EPA ISA) to determine which health endpoints are causally related to Pb exposures (U.S. EPA, 2013b). Additionally, the National Toxicology Program (NTP) summarized its findings on the weight of evidence relating low-level Pb exposure to adverse health outcomes in the *Monograph on Low-Level Lead Exposure* (hereafter referred to as the NTP Monograph). If an endpoint is deemed to not be associated with Pb exposure, it would be inappropriate to conduct a benefits analysis that included that endpoint. Thus, we focus on endpoints with the highest weight of evidence assessments in the EPA ISA and NTP Monograph. For the purposes of this report, we focus only on CVD mortality; additional CVD morbidity endpoints will be addressed in subsequent reports.

Section 2 of this report describes the epidemiological evidence and conclusions on the association between Pb exposures and effects on the cardiovascular system in the EPA ISA and NTP Monograph. In Section 2.3 we describe our methodology for identifying studies and summarize the identified studies. Section 4 presents our methods and results for selecting key studies that may inform the quantitative relationship between Pb and CVD mortality. Additionally, in this section we provide an example application of our concentration-response function and corresponding health impact model. In Section 5 we discuss the generalizability of the concentration response function. Section 6 discusses uncertainty and variability in the functions developed. Our conclusions are presented in Section 7.

2. Conclusions on the Association between Pb Exposures and CVD Mortality

In order to include quantified benefits associated with reduced Pb exposure for a specific endpoint in a rulemaking, one needs to be able to reasonably conclude from the available scientific evidence that the endpoint is associated with the Pb exposure. In this section, we provide justification for our decision that there is sufficient weight-of-evidence to connect Pb exposure in adults with increased CVD mortality risk. In Section 2.1, we introduce the key government documents reviewed (the EPA ISA and NTP Monograph) to assess weight of evidence. We then discuss the conclusions made in the key documents for the endpoints of CVD mortality (Section 2.2). In Section 2.3, we lay out evidence on the potential mechanisms by which Pb exposure can cause CVD related mortality.

2.1 Summary of Government Documents that Evaluated Weight of Evidence for Adverse Effects Related to Pb Exposure

There are two recent, comprehensive government documents that summarize the literature and provide weight-of-evidence assessments for the adverse health effects of Pb exposure: the EPA ISA (U.S. EPA, 2013) and the NTP Monograph (National Toxicology Program, 2012). In Sections 2.1.1 and 2.1.2, we explain the methods and terminology in the EPA ISA and the NTP Monograph, respectively, in further detail.

2.1.1 EPA ISA

The EPA ISA report surveyed and evaluated policy-relevant science examining the relationship between Pb and human health. The report determined causality between Pb exposure and adverse health outcomes by an evaluation and synthesis of evidence from epidemiologic and toxicological studies published since the last EPA review in 2006. Based on evaluation 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 certain health outcomes affecting the nervous, cardiovascular, hematologic, and reproductive and developmental systems (U.S. EPA, 2013). The EPA ISA also determined a likely causal relationship between Pb exposure and cancer, as well as several effects on the immune system (U.S. EPA, 2013).

2.1.2   The NTP Monograph

The NTP Monograph summarizes the entire epidemiologic body of evidence for human health effects associated with low-level Pb exposure (blood Pb levels <10 µg/dL). This monograph does not focus on health effects at blood Pb levels >10 µg/dL (National Toxicology Program, 2012). 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, 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

In children, NTP found sufficient evidence for several adverse health endpoints associated with blood Pb levels <10 µg/dL: decreased IQ, delayed puberty, reduced growth, increased attention-related issues, increased problem behaviors, and decreased hearing. In adults, there was judged to be sufficient evidence for an association between blood Pb <10 µg/dL and the endpoints of increased blood pressure, hypertension, tremor, and decreased glomerular filtration rate. At these blood Pb levels, NTP also found sufficient evidence of reduced fetal growth given prenatal exposures to Pb.

2.2 EPA ISA and NTP Monograph Findings on Cardiovascular Disease Mortality

The endpoint of CVD mortality was examined in the EPA ISA (under the category of coronary heart disease) and the NTP Monograph. A summary of the conclusions from the EPA ISA and NTP Monograph for CVD mortality is presented in Exhibit 2.

Exhibit 2. Conclusions from the EPA ISA and NTP Monograph on CVD Mortality in Adults Associated with Pb Exposure

Effect	Definition	EPA ISA Conclusion	NTP Conclusion
CVD mortality	Death attributed to heart or circulatory causes	Included in *causal* determination for coronary heart disease. 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, 2013b)

The EPA ISA deemed the association between Pb exposure and coronary heart disease (including CVD 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, 2013b).

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…" (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, both studies have limitations that may have biased the results. Additional discussion of these two studies can be found in Appendix A: Discussion of Møller and Kristensen (1992) and Weisskopf et al. (2009)

2.3   Mechanisms by Which Pb Impacts Cardiovascular Health

The mechanism by which Pb impacts cardiovascular health and consequently increases risk of CVD mortality is one which has been researched for decades but is still being elucidated (Kopp, Barron, & Tow, 1988; Vaziri 2008, Roy and Kordas, 2016). This section provides an overview of the multiple mechanisms through which Pb is thought to influence CVD mortality. For more information on the mode of action for the cardiovascular effects of Pb, the reader is referred to pages 4-324 through 4-404 of EPA's ISA report (U.S. EPA, 2013b).

Pb can operate through multiple mechanisms. This includes increasing oxidative stress, disrupting homeostasis of hormones or other molecules which regulate the body's cardiovascular system, mimicking calcium in important cellular functions, damaging the endothelium of the vasculature, disrupting angiogenesis (i.e., the development of new blood vessels) and/or directly impacting the heart. Additional information on each of these mechanisms follow in the subsequent paragraphs. This summary is based on information presented in both the EPA ISA and Vaziri (2008). Much of the information on these mechanisms comes from toxicological or occupational studies.

2.3.1   Oxidative Stress and Hypertension

One of the most heavily researched mechanisms by which Pb is known to harm the cardiovascular system is by causing oxidative stress.[1] Specifically hypertension (i.e., increased blood pressure), which contributes to CVD mortality risk, can be attributed to Pb-induced oxidative stress. This is supported by studies in which animals exposed to Pb experience hypertension. Once treated with strong antioxidants, these animals had their blood pressure return to normal, demonstrating the hypertension was due to oxidative stress induced by Pb (Khalil-Manesh et al., 1994; N. Vaziri, Ding, Ni, & Gonick, 1997). Further, additional studies have shown an increase in the markers of oxidative stress in Pb-exposed animals that experienced hypertension (Farmand, Ehdale, Roberts, & Sindhu, 2005; N. Vaziri, Lin, Farmand, & Sindhu, 2003).

The oxidative stress caused by Pb exposure can result in increased hypertension and risk of CVD mortality through several mechanisms. For example, reactive oxygen species can inactivate and sequester nitric oxides (Ding, Vaziri, & Gonick, 1998; Dursun, Arifoglu, Suer, & Keskinol, 2005; Gonick, Ding, Bondy, N, & Vaziri, 1997). Nitric oxides are potent vasodilators therefore when

---

[1] Reactive oxygen species are produced as a result of normal cellular metabolism. As explained by Birben et al. (2012), "the shift in balance between oxidant/antioxidant in favor of oxidants is termed oxidative stress." Specifically, "at low to moderate concentrations, [reactive oxygen species] function in physiological cell processes, but at high concentrations, they produce adverse modifications to cell components, such as lipids, proteins, and DNA... Oxidative stress contributes to many pathological conditions, including cancer, neurological disorders, atherosclerosis, hypertension, ischemia/perfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and asthma" (Birben et al., 2012, p. 9).

inactivated there is a constriction of blood vessels, leading to increased blood pressure and increasing one's risk of CVD mortality (N. D. Vaziri, 2008). Additionally, oxidative stress can also cause increases in inflammation. Inflammation in the kidney, which plays a key role in regulating blood pressure, can also contribute to increased blood pressure or other cardiovascular disease and subsequently increase risk of CVD related mortality (N. D. Vaziri, 2008).

Roy and Kordas (2006) evaluated low-level Pb exposure and oxidative stress in both children and non-occupationally exposed adults by conducting a systematic evaluation of the literature. In the majority of papers summarized by the authors, there was an association noted between the biomarkers of Pb exposure and the markers of oxidative stress. However, the authors found the quality of evidence on the topic to be lacking due to lack of covariate control in many studies, and a diversity of biomarkers examined both for lead exposure and of oxidative stress.

2.3.2   Hormone and Other Signaling Molecule Disruption

In addition to causing oxidative stress, Pb has been implicated in having impacts on hormones which regulate the constriction and contraction of blood vessels and also regulate body fluid volume, causing disruptions which could lead to increased risk of CVD mortality. For example, in an occupational study of workers exposed to Pb, Chang et al. (2006) found high levels of norepinephrine, a hormone which can increase blood pressure via receptors on the vasculature. Additional studies in rats with Pb-induced hypertension also demonstrated that Pb can have other impacts on the sympathetic nervous system by altering certain receptors in the vasculature and kidney, as well as by inactivating nitric oxides. These alterations may have cascading effects which can result increased vasoconstriction and activation of the renin-angiotensin system (RAAS)[2], which further increases blood pressure and risk of cardiovascular disease related mortality. (H. Chang et al., 1997; Tsao, Yu, Cheng, Ho, & Chang, 2000, Campese, Sindhu, Ye, Vaziri, & Jabbari, 2007).

Further, given Pb is similar in charge and size to calcium, it is unsurprising that studies have found that Pb competes with calcium in various transport systems into and out of cells and has been shown to interact with key calcium dependent signaling pathways (Chai & Webb, 1988; Habermann, Crowell, & Janicki, 1983; Richardt, Federolf, & Habermann, 1986; Simons, 1993a, 1993b; Watts et al., 1995).   Given calcium plays a vital role in regulating vascular tone and arterial pressure, this is an additional mechanism through which Pb may impact cardiovascular health and increase risk of CVD related mortality. There is also evidence from toxicological and occupational studies that Pb can impact proteins and lipid levels that also help regulate the vasculature system. Pb exposure disrupts the homeostasis of these molecules, resulting in

---

[2] "The renin-angiotensin aldosterone system (RAAS) is a hormonal cascade that functions in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. Dysregulation of the RAAS plays an important role in the pathogenesis of cardiovascular and renal disorders" (Atlas, 2007, p. S9)

increased blood pressure and risk of other cardiovascular disease, which can contribute to increased risk of CVD related mortality.

2.3.3   Disruption of Endothelial Lining, Growth and Repair & Angiogenesis

Evidence suggests Pb can damage endothelial lining and also disrupt the endothelial growth and repair process (Kaji et al., 1995; Kaji et al., 1992). The endothelial lining prevents blood coagulation and ensures blood fluidity. Therefore, damage to the endothelium can result in atherosclerosis, thrombosis and tissue injury, all of which may contribute to CVD mortality. This may partially be a result of oxidative stress described in Section 2.3.1. Further, Pb has also been shown to disrupt angiogenesis. Given that disruptions in angiogenesis can exacerbate atherosclerotic ischemic disease, this also may be a mechanism through which Pb increases risk from CVD mortality (Lahteenvuo & Rosenzweig, 2012). *In vitro* angiogenesis assays exposed to Pb acetate demonstrated inhibition of tube formation in human endothelial cells (Kishimoto, Oguri, Ueda, & Tada, 1995; Ueda, Kishimoto, Dekio, & Tada, 1997) in a concentration and time dependent manner. Pb citrate was also observed to cause hyperplasia[3] in rat aorta smooth muscles (Carsia, Forman, Hock, Nagele, & McIlroy, 1995). These studies demonstrate Pb may simulate events that can evolve into atherosclerosis, which further increases risk of CVD related mortality.

2.3.4   Direct Impact on the Heart

There is also evidence that Pb may directly impact the heart. In a study of exposure to a solution containing Pb acetate, an isolated rat heart showed prolonged conduction times, lowered coronary blood flow and reduced heart rate (Prentice & Kopp, 1985). These direct effects were observed at 30 µM Pb acetate, with milder responses being seen at 0.3 µM (Prentice & Kopp, 1985).

2.3.5   Summary

Based on the evidence presented, it is clear there are several mechanisms through which Pb may impact cardiovascular health. Although the literature on general population exposure and mechanisms of toxicity are limited, an understanding of how Pb may increase CVD mortality can be gleaned from the existing toxicological, occupational and *in vitro* studies. Specifically, it is clear Pb may increase CVD mortality through a variety of mechanisms including indirect impacts (e.g., increasing oxidative stress, disturbing hormone homeostasis, disrupting calcium signaling) for which the cascading impacts (e.g., increased blood pressure, atherosclerosis) can adversely impact cardiovascular health. There is also evidence that Pb can directly impact cardiovascular health through mechanisms such as damaging the endothelial lining, causing dose-dependent increases in vasoconstriction and impacting heart performance directly. As discussed in Section 5.3, Pb in the body may be a result of recent exposures (i.e., within the last 30 days) or endogenous exposures due to re-release of Pb from bone. Further, although some mechanisms

---

[3] Increased cell production in a normal tissue or organ (MedlinePlus, 2019)

are direct and some are indirect, there is not enough information in the available literature on the timing or duration of exposure that would result in increased CVD related mortality risk. It is likely that both short and longer term exposures can be important. It is clear that there are mechanisms by which Pb adversely impacts the cardiovascular system and can subsequently increase risk from CVD mortality.

3. Assessment of the 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. This chapter summarizes our approach to locating and assessing the literature to identify a key study (or studies). Specifically, Section 3.1 describes our approach to identifying potential key studies and provides an overview of studies on the association between Pb and CVD mortality that were excluded from further consideration. We describe the eight potential key studies identified in greater detail in Section 3.2.

3.1   Identification of Potential Key Studies

A large body of literature exists on the adverse health effects of Pb exposure. The EPA's ISA and the NTP Monograph provide an initial summary through 2011 (National Toxicology Program, 2012; U.S. EPA, 2013b); we used these documents to identify an initial set of studies that could serve as the basis of a concentration-response function relating Pb exposure to CVD mortality. Eight studies were identified for full-text review.

We also conducted a supplemental primary literature search using PubMed to identify studies published after the EPA ISA's last literature search date (September 2011) through May 14, 2018.

The following search string was used:

> ((lead[MeSH Terms] OR pb OR "lead exposure" OR "bone lead" OR " tibia lead" OR "patella lead" OR "blood lead") AND ((Cardiovascular Diseases[MeSH Terms] AND mortality) OR (cardiovascular disease mortality) OR (CVD mortality) OR (cardiovascular mortality)) AND ("2011/09/01"[Date - Publication] : "3000"[Date - Publication]))

Given that the majority of the evidence relating Pb exposure to CVD mortality is based on blood Pb levels as the biomarker, and that the well-accepted pharmacokinetic models (e.g., Leggett, 1993; U.S. EPA, 1996) have limited capability to predict and validate bone Pb levels, in this analysis we concentrate solely on studies using blood Pb as the biomarker of exposure.[4]

To determine the applicability of studies identified in the supplemental literature review, we first reviewed titles and abstracts. Titles indicating that the study was conducted in humans, included an evaluation of Pb exposure, and researched adverse cardiovascular outcomes were passed through to abstract review. If it was unclear if the paper had these attributes, we moved the paper on to abstract review. Abstract review consisted of evaluating whether the paper assessed the association between blood Pb exposure and CVD mortality in adults. If the paper

---

[4] Note: Since we used a broad scope for our initial search, our search string includes bone Pb; however, we chose to focus on blood Pb studies in this report because these studies are more useful for quantifying benefits.

passed through abstract review, it was then subject to full-text review. Seven studies were identified for full-text review from our supplemental literature search. In total, 15 studies on the association between blood Pb and CVD mortality were identified for full-text review.

Next, we narrowed down the number of studies for full-text review by assessing each article against the following two criteria: (1) the study was published in a peer-reviewed journal and (2) the mean blood Pb level in the study was less than 10 µg/dL. This resulted in the exclusion of 7 of the 15 studies. The excluded studies are summarized in Exhibit 4, along with the justification for exclusion. Additional details on the remaining 8 studies are presented in Section 3.2.

Exhibit 3.   Overview of Literature Review Approach and Results

Step 1: Identify Universe of Studies

Unique Studies in EPA ISA and/or NTP Monograph (n=8)

Supplemental Literature Search using PubMed (n=7)

15 Studies on Pb Exposure/CVD Mortality Data Identified
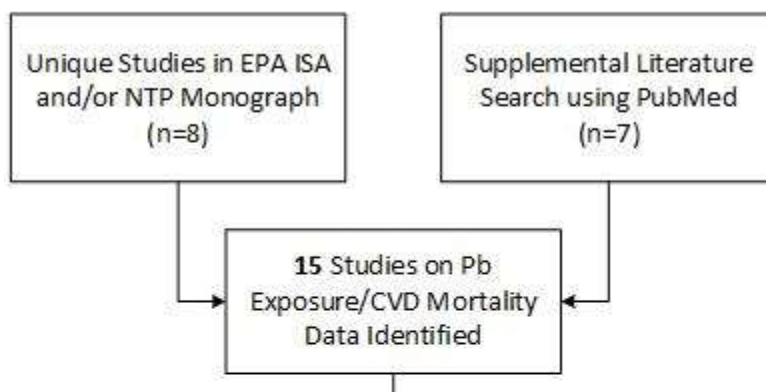
Step 2: Remove Studies Based on Initial Criteria

7 Studies Excluded
- No BLL data
- BLL > 10 µg/dL
- Not Representative of General U.S. Population

8 Studies Met Inclusion Criteria
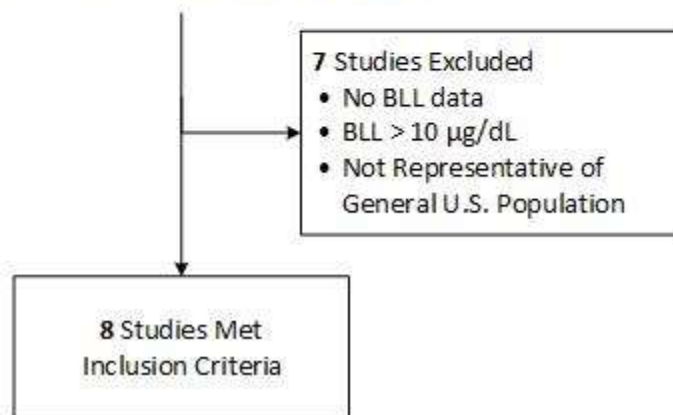
Exhibit 4. **Summary of Studies Excluded Based on Initial Criteria**

Study	Population	Mean Blood Lead Level (unless otherwise stated)	Key Finding	Justification for Exclusion
Bertke et al. (2016) *Mortality of Lead Smelter Workers: A Follow-Up Study With Exposure Assessment*	1,990 male Pb smelters in Idaho	Not measured	Standardized mortality ratios (SMRs) for the Pb smelters' deaths from CVD were elevated compared to the general population of Idaho (SMR 1.22, 95% CI: 1.13, 1.31) but not across the US (SMR 1.02, 95% CI: 0.95, 1.09). CVD deaths also increased with estimated cumulative Pb exposure.	There is no blood Pb measurement.
Cocco et al. (2007) *Causes of death among lead smelters in relation to the glucose-6-phosphate dehydrogenase polymorphism*	933 male Pb smelters in Sardinia, Italy	Not measured	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 Pb smelters with the general population.	There is no blood Pb measurement.
Lin et al. (2011) *Association of blood lead levels with mortality in patients on maintenance hemodialysis*	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.	Median: 10.4 μg/dL	Baseline BLLs >12.64 μg/dL associated with higher cardiovascular-caused mortality (HR = 9.71; 95% CI = 2.11-23.26), in patients over 18 months of follow-up	Central estimate of blood Pb > 10 μg/dL.

Study	Population	Mean Blood Lead Level (unless otherwise stated)	Key Finding	Justification for Exclusion
Lustberg & Silbergeld (2002) *Blood lead levels and mortality*	4,292 participants from NHANES II (1976-1980)	14.0 ± 5.1 µg/dL.	Adults with BLLs 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.	Mean blood Pb > 10 µg/dL.
Neuberger et al. (2009) *Potential health impacts of heavy-metal exposure at the Tar Creek Superfund site, Ottawa County, Oklahoma*	Residents of five Ottawa County towns located within the boundaries of the Tar Creek Superfund site (i.e., the exposed area) compared to residents of four Ottawa County towns not within the boundaries of the Tar Creek Superfund site (i.e., the unexposed area).	Not measured	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).	There is no blood Pb measurement.
McElvenny et al. (2015) *Mortality of a cohort of workers in Great Britain with blood lead measurements*	British Health and Safety Executive data of 1,368 workers in Great Britain with measured BLLs and circulatory system diseases	44.3 µg/dL	The SMR for mortality due to circulatory system diseases compared to data for the rest of the country was 105 (95%CI: 99-110) for this population.	Mean blood Pb > 10 µg/dL.

Study	Population	Mean Blood Lead Level (unless otherwise stated)	Key Finding	Justification for Exclusion
Wang et al. (2011) *Long-term heavy metal pollution and mortality in a Chinese population: an ecologic study*	1,152 local residents in China in high-heavy metal exposure areas (Shangba, Xiaozhen, Dongfang) versus low-heavy metal exposure areas (six villages)	17.8 μg/dL[a]	The mortality rate from CVD in the highly exposed area was significantly elevated compared with the lower exposed area.	Mean blood Pb > 10 μg/dL
BLL = blood lead level; CI = confidence ratio; CVD = cardiovascular disease; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; SMR = standardized mortality ratio [a]No overall mean or median blood Pb level was presented in Wang et al. (2011). This value is a calculated weighted mean blood Pb level based on the cohort population characteristics presented in Table 2 of Wang et al. (2011).				

3.2   Summary of Potential Key Studies

The eight studies that remained after applying our initial inclusion criteria were:

- Aoki et al. (2016) *Blood Lead and Other Metal Biomarkers as Risk Factors for Cardiovascular Disease Mortality*

- Khalil et al. (2009) *Association of blood lead concentrations with mortality in older women: a prospective cohort study*

- Lanphear et al. (2018) *Low-level lead exposure and mortality in US adults: a population-based cohort study*

- Menke et al. (2006) *Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults*

- Ruiz-Hernandez et al. (2017) *Declining exposures to lead and cadmium contribute to explaining the reduction in cardiovascular mortality in the US population, 1988-2004*

- Schober et al. (2006) *Blood Lead Levels and Death from All Causes, Cardiovascular Disease, and Cancer: Results from the NHANES III Mortality Study*

- Weisskopf et al. (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*

- Weisskopf et al. (2015) *Biased Exposure-Health Effect Estimates from Selection in Cohort Studies - Are Environmental Studies at Particular Risk?*

A summary of each study is provided in the subsequent sections.

3.2.1   Aoki et al. (2016)

The purpose of Aoki et al. (2016) was to "examine the blood Pb-CVD mortality association with hematocrit/hemoglobin-corrected blood lead using NHANES 1999 to 2010" (p. 1). The authors opted to use the hematocrit[5] or hemoglobin[6] corrected values of blood Pb in order to test the hypothesis that hematocrit/hemoglobin-corrected blood Pb levels are better biomarkers of exposure for Pb than whole blood Pb. This is because the majority of blood Pb is in red blood cells; if Pb causes total red blood cell count to decrease (i.e., Pb-induced anemia), there will be an underestimation of the relationship between blood Pb and CVD mortality. To explore this idea, Aoki et al. (2016) used data on 18,602 individuals, 40 years of age and older, from the 1999-2010 National Health and Nutrition Examination Survey (NHANES). Exhibit 5 describes the mean whole, hemoglobin- and hematocrit- corrected blood Pb levels in this subset of the NHANES population. Follow-up occurred from the date of NHANES examination through December 31, 2011. Deaths were identified by reviewing death records for International

---

[5] Percentage of the volume of whole blood that is made up of red blood cells (MedlinePlus, 2014a)

[6] A protein in red blood cells that carries oxygen (MedlinePlus, 2014b)

Classification of Diseases 10 codes I00-I99, which correspond to CVD mortality. In this population there were 985 CVD deaths with a median follow up time of 6.2 years.

Exhibit 5.   Mean Whole Blood Pb and Corrected for Red Blood Cell Concentration Blood Pb Levels (Aoki et al., 2016)

Variable	Geometric Mean (µg/dL) (SE)
Whole blood Pb	1.73 (0.02)
Hematocrit-corrected blood Pb	1.73 (0.02)
Hemoglobin-corrected blood Pb	1.74 (0.02)

To model the relationship between blood Pb and CVD mortality, Aoki et al. (2016) used a Cox proportional hazard regression analysis, with age during follow-up (as opposed to elapsed time since enrollment in the cohort) as the time scale. The authors used three blood Pb measurements as the main exposure variable in three separate models: (1) hematocrit-corrected blood Pb; (2) hemoglobin-corrected blood Pb; and (3) (uncorrected) whole blood Pb. To correct for hematocrit/hemoglobin, the authors divided whole blood Pb by the hematocrit and hemoglobin concentration measured in NHANES. Aoki et al. then multiplied the corrected blood Pb variable by the weighted geometric mean of hematocrit and hemoglobin, respectively, in the analytic sample so that results for the corrected variables would be comparable to those for whole blood.

In addition to exploring the association of hematocrit/hemoglobin corrected blood Pb with CVD mortality, Aoki et al. (2016) also examined several variables as confounders in the blood Pb-CVD mortality relationship. To be a confounder, a variable must be independently associated with the exposure of interest (i.e., blood Pb) and the outcome of interest (i.e., CVD mortality). Aoki et al. (2016) considered the standard confounders that are often included in analyses related to Pb exposure and adverse health outcomes, such as demographic data (race/Hispanic origin and sex), smoking status (never, former and current), education (less than high school, high school, and college or higher), and alcohol intake (number of drinks per week). The authors also evaluated non-Pb biomarkers as confounders. The non-Pb biomarkers assessed as confounders are listed below, along with justification for inclusion:

- Blood cadmium: cigarette smoke, a known contributor to CVD mortality, contains both cadmium and Pb. Additionally, cadmium alone has been associated with CVD mortality (Messner & Bernhard, 2010; Tellez-Plaza et al., 2013). The authors included this variable to represent a mixture of nontobacco sources and smoking intensity within former and current smokers.
- Serum iron: Iron deficiency is known to cause increased absorption of Pb, and iron deficiency and anemia are risk factors for CVD mortality.
- Serum C-reactive protein: Serum iron decreases in the presence of inflammation. To avoid the serum iron-CVD mortality association from reflecting a direct inflammation-

CVD mortality association, C-reactive protein was included because it is a marker of inflammation.

- Serum calcium: Calcium deficiency can result in increased Pb absorption (Holstege, Huff, Rowden, O'Malley, & Ramachandran, 2015) and serum calcium may be associated with CVD risk (Lutsey et al. (2013) as cited by Aoki et al., 2016).
- Bone Mineral Density: Included because it is a proxy for long term calcium status. As stated above, calcium deficiency is a potential confounder of the association.

When entering the confounders and blood Pb measurements into the model, all of the right-skewed variables (i.e., the three blood Pb measurements, blood cadmium and C-reactive protein) were log-transformed.

Additionally, to test for nonlinearity in the model "continuous independent variables, except for alcohol consumption were initially entered into Cox regression as 5 knot natural spline terms" (p. 5). The authors modeled alcohol consumption with a quadratic function. A Wald test for coefficients of nonlinear spline terms was implemented. The results of this analysis indicated little evidence for non-linearity between the log-transformed blood Pb measurements and CVD mortality. However, serum iron and serum calcium exhibited a U shaped, non-linear relationship with CVD mortality.

To demonstrate the nature and magnitude of the confounding due to non-Pb biomarkers, the authors conducted multiple models for each blood Pb measurement, where each non-Pb biomarker (i.e., blood cadmium, serum iron, C-reactive protein, and serum calcium) was removed from the fully model adjusted model. In addition, the authors also conducted models in which they adjusted for hemoglobin or hematocrit instead of correcting for it. In the "adjusted for" models, both whole blood Pb and the red blood cell concentration (i.e., hemoglobin or hematocrit) are included in the regression model. This is in contrast to the "corrected for" model in which the ratio of whole blood Pb to hemoglobin/hematocrit is a single variable in the regression equation. Lastly, the authors also conducted each of the fully adjusted models on a subset of the NHANES population (n=10,264) with bone mineral density (BMD) measures and included BMD as an additional adjustment in the model.

To assist in interpreting the large number of models conducted, Aoki et al. assigned each model a code, denoted with a letter and a number. The letter designates the blood Pb variable with "A" indicating hematocrit-adjusted blood Pb, "B" indicating hemoglobin-adjust blood Pb and "C" indicating whole blood Pb. The numbers indicate which confounders are adjusted for in the models. Specifically, "1" indicates the fully adjusted model, the "2-7" models were those where 1 or 2 of the non-Pb biomarkers were dropped, the "8" model includes the BMD and the "9" model are the models where hemoglobin and hematocrit were adjusted for as opposed to corrected for, as explained above. Results of Aoki et al. (2016) are presented in Exhibit 6.

Exhibit 6. **Adjusted Relative Risk for Cardiovascular Mortality from Models with Varying Correction for Blood Pb and Adjustment for Other Covariates: NHANES 1999 to 2010 with Mortality Follow-Up through 2011 (Aoki et al., 2016)**

Model*	Blood Pb	Blood Cadmium	Serum Iron†	C-Reactive Protein	Serum Calcium†	Bone Mineral Density‡	Red Blood Concentration
Models with hematocrit-corrected blood Pb or with hematocrit adjustment							
A0	1.81 (1.33–2.45)	None	None	None	None	None	None
A1§	1.44 (1.05–1.98)	1.35 (1.15–1.59)	0.005	1.37 (1.12–1.68)	0.005	None	None
A2	1.65 (1.21–2.25)	None	0.007	1.40 (1.15–1.71)	0.002	None	None
A3	1.53 (1.12–2.10)	1.34 (1.13–1.57)	None	1.56 (1.29–1.90)	4×10^{-4}	None	None
A4	1.42 (1.03–1.95)	1.37 (1.17–1.61)	1×10^{-5}	None	0.005	None	None
A5	1.45 (1.06–1.99)	1.37 (1.17–1.61)	0.002	1.36 (1.12–1.66)	None	None	None
A6	1.74 (1.28–2.37)	None	None	1.59 (1.32–1.92)	3×10^{-4}	None	None
A7	1.55 (1.12–2.13)	2.07 (1.43–2.99)	None	None	9×10^{-5}	None	None
A8‖	1.46 (1.00–2.11)	1.34 (1.08–1.66)	0.21	1.38 (1.04–1.84)	0.007	0.28 (0.10–0.78)	None
A9	1.35 (0.98–1.86) ¶	2.22 (1.56–3.18)	0.08	1.39 (1.14–1.71)	0.005	None	0.67 (0.54–0.81)#
Models with hemoglobin-corrected blood Pb or with hemoglobin adjustment							
B0	1.84 (1.36–2.50)	None	None	None	None	None	None
B1§	1.46 (1.06–2.01)	1.35 (1.15–1.58)	0.005	1.37 (1.12–1.68)	0.005	None	None
B2	1.67 (1.23–2.28)	None	0.008	1.40 (1.15–1.71)	0.002	None	None
B3	1.56 (1.14–2.14)	1.33 (1.13–1.57)	None	1.56 (1.29–1.90)	4×10^{-4}	None	None
B4	1.44 (1.05–1.98)	1.37 (1.17–1.60)	1×10^{-5}	None	0.005	None	None
B5	1.47 (1.07–2.02)	1.37 (1.17–1.61)	0.002	1.36 (1.12–1.66)	None	None	None
B6	1.77 (1.31–2.41)	None	None	1.59 (1.32–1.92)	3×10^{-4}	None	None
B7	1.58 (1.15–2.17)	2.06 (1.43–2.97)	None	None	9×10^{-5}	None	None
B8‖	1.48 (1.02–2.14)	1.34 (1.08–1.66)	0.22	1.38 (1.04–1.84)	0.007	0.28 (0.10–0.79)	None
B9	1.35 (0.98–1.87) ¶	2.24 (1.57–3.20)	0.17	1.40 (1.14–1.71)	0.005	None	0.63 (0.51–0.76)**
Models with whole blood Pb without hematocrit/hemoglobin correction or adjustment							
C0	1.53 (1.11–2.11)	None	None	None	None	None	None
C1*	1.27 (0.91–1.78)	1.36 (1.16–1.60)	0.003	1.37 (1.11–1.68)	0.005	None	None
C2	1.49 (1.08–2.06)	None	0.004	1.40 (1.15–1.71)	0.002	None	None
C3	1.30 (0.93–1.82)	1.35 (1.15–1.59)	None	1.57 (1.29–1.90)	3×10^{-4}	None	None
C4	1.27 (0.91–1.76)	1.38 (1.18–1.62)	5×10^{-5}	None	0.005	None	None
C5	1.28 (0.92–1.78)	1.38 (1.18–1.62)	0.001	1.36 (1.11–1.66)	None	None	None

C6	1.51 (1.09–2.10)	None	None	1.60 (1.33–1.93)	2×10^{-4}	None	None
C7	1.29 (0.92–1.81)	1.39 (1.18–1.63)	None	None	7×10^{-5}	None	None
C8[‖]	1.31 (0.89–1.93)	2.00 (1.22–3.27)	0.17	1.38 (1.03–1.83)	0.006	0.28 (0.10–0.78)	None

Relative risk per 10-fold increase and its 95% CI presented unless otherwise indicated. Adjusted for sex, race/Hispanic origin, smoking, and alcohol consumption.

CI = confidence interval, NHANES = National Health and Nutrition Examination Survey.

[*]Each model is given a code for easy reference in the text.

[†]Modeled using natural spline therefore no single summary hazard ratio can be presented. Instead P-values for the set of natural spline terms are presented.

[‡]Relative risk per unit (g/cm2) increase and its 95% CI presented.

[§]Models A1 and B1 were fully adjusted and fit to the analytic sample.

[‖]Models A8 and B8 were fit to a subset of the analytic sample due to limited availability for multiply imputed bone mineral density data.

[¶]Whole blood Pb.

[#]Relative risk per 10% increase in hematocrit and its 95% CI.

[**]Relative risk per 10% increase in hemoglobin and its 95% CI.

Source: Aoki et al. (2016, Table 2)

Exhibit 6 demonstrates that hematocrit/hemoglobin-corrected blood Pb variables are similarly associated with CVD mortality. Additionally, comparing the results from the fully adjusted ("1") model across exposure variables, it can be seen that not correcting for red blood cell concentration (i.e., the "C" models) can result in an underestimate of the risk of CVD mortality. This is exemplified by the fact that the hazard ratio associated with a 10-fold increase in hematocrit- or hemoglobin-corrected blood Pb levels is 1.44 (model A1) or 1.46 (model B1), respectively, both with confidence intervals that do not include 1. However, the hazard ratio for whole blood Pb and CVD mortality is 1.27 (model C1) with a confidence interval that does encompass the null value of 1. This pattern, with whole blood Pb underestimating the relationship with CVD mortality, persists through the models.

An additional notable pattern is that when blood cadmium (model 2) and serum iron (model 3) are excluded from the model, the relative risk increases. The authors interpret this finding as evidence that not adjusting for these variables would result in residual confounding, which could result in an overestimate of the relationship between blood Pb and CVD mortality. Removing both serum iron and C-reactive protein (model 7) did not dramatically increase the relative risk, compared to when only serum iron was removed (model 3). Therefore, C reactive-protein was not operating as a strong confounder in this study. Serum calcium also does not appear to be acting as a strong confounder (model 5), because removing it from the model does not dramatically shift the relative risk estimate. Additionally, including BMD in the model (model 8) also did not greatly impact the hazard ratio. Lastly, the adjustment (rather than correction) for hematocrit/hemoglobin resulted in a lower hazard ratio (model 9). The authors argue that "if red blood cell concentration acted as an intermediate variable in the causal pathway between exposure to Pb and mortality then the lead exposure's effects would have been absorbed into the coefficient representing the association between low red blood concentration and mortality. In fact, we found that the adjusted hazard ratios were attenuated compared to the corresponding hazard ratios for hematocrit/hemoglobin-corrected blood lead." According to Aoki et al. (2016), this is likely due to uncontrolled confounding due to pre-existing anemia (p. 6).

3.2.2   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 (SOF). Participants were originally recruited into the SOF from 1986 to 1988 using population based listings in Baltimore, MD, Minneapolis, MN, Portland, OR and Pittsburgh, PA. The Pb ancillary study was conducted in 1990-1991 using only participants from Pittsburgh or Baltimore and consisted of 533 white women aged 65–87 years old. The aim of this study was to evaluate blood Pb levels in association with all-cause and cause-specific mortality.

The mean blood Pb concentration of the sample was 5.3 ± 2.3 μg/dL. Initially, 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 elevated 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. In addition to blood Pb testing, participants underwent a physical examination and completed a questionnaire and interview regarding health and lifestyle factors. After the examination, participants were followed up with via mail three times per year throughout a follow-up period of 12 (± 3) years. 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. Based on biological plausibility and prior research, the authors selected the following confounders for inclusion in the model: age increase per 5 years, clinic, BMI, education, smoking, alcohol intake, estrogen use, hypertension, total hip BMD, walking for exercise, and diabetes. Their findings are summarized in Exhibit 7.

Exhibit 7.   Hazard Ratios and 95% Confidence Intervals of All-Cause Mortality by Blood Pb Concentrations (Khalil et al., 2009)

Cause of Death	Deaths	Blood Pb Concentration (μg/dL) [μmol/L]		P$_{value}$
		(< 8) [< 0.384]	(≥ 8) [≥ 0.384]	
All cause death, n (%)	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 provide evidence for the association between Pb exposure and CVD mortality in a portion of the adult U.S. population, the p value indicates this relationship is borderline statistically significant for the multivariate adjusted model. It is possible that there is some selection bias in this study. This is because, during the time between recruitment of the SOF cohort and the Pb ancillary study, there may be a loss to follow-up of individuals most at risk for cardiovascular disease. The potential for this bias is evidenced by the fact that there was a statistically significant difference in the number of participants with hypertension in the SOF (39%) compared to the Pb ancillary study (29%). However, it is clear by evaluating the hazard ratios that there is a consistent relationship between higher blood Pb and death due to various causes.

3.2.3   Lanphear et al. (2018)

In their paper *Low-level lead exposure and mortality in US adults: a population-based cohort study,* Lanphear et al. (2018) aimed to estimate the relative contribution of Pb exposure to all-cause and CVD mortality using a nationally representative sample from NHANES-III. Additionally, the authors aimed to expand upon findings on the association between Pb and CVD mortality from Menke et al. (2006) by using a longer duration of follow-up. Participants in the study were enrolled in NHANES from 1988 to 1994 and were aged 20 years or older at baseline. NHANES conducted household interviews to obtain demographic information from participants. Participants also underwent medical examinations, during which health information (e.g., BMI, alcohol consumption) and blood and urine samples were collected. Samples were analyzed for concentrations of Pb, cadmium, and creatinine. For the blood Pb analyses, the limit of detection (LOD) was 1.0 µg/dL. Study participants with blood Pb levels below the LOD were assumed to have blood Pb of 0.7 µg/dL (i.e., the LOD divided by the square root of 2). Follow-up of all participants occurred through December 31, 2011; personal identifiers (e.g., birth date, social security number) were used to link participants to National Death Index data up to this date. Based on ICD codes, deaths from all causes, CVD (ICD-9 codes 390-459; ICD-10 codes I00-I99), and ischemic heart disease (ICD-9 codes 410-414; ICD-10 codes I20-I25) were identified.

In the statistical analyses, the authors weighted results to account for the oversampling methods used in NHANES-III. Cox proportional hazards models were used to calculate hazard ratios (HRs) for the associations between continuous blood Pb and the three types of mortality. Additionally, the shape of the dose-response relationships between Pb and the three types of mortality were investigated using five-knot restricted cubic splines. Analyses were adjusted for variables known to be potential confounders for CVD mortality: age, sex, income, ethnicity, BMI, smoking status, alcohol consumption, physical activity, urinary cadmium levels, blood pressure, glycated hemoglobin, and cholesterol. The authors used population attributable fractions to estimate the proportional reduction in mortality that would occur if blood Pb levels decreased to 1.0 µg/dL in all U.S. adults aged 20 years and above. They additionally investigated the effects of low-level Pb exposures by restricting analyses to participants with blood Pb levels below 5.0 µg/dL.

The study analyzed information on 14,280 individuals from NHANES-III. The geometric mean blood Pb level was 2.71 µg/dL, and 9% (1150) of participants had blood Pb below the LOD of 1 µg/dL. During the follow-up period (median of 19.3 years), 4422 participants died. Of these deaths, 38% were attributable to CVD and 22% to ischemic heart disease. Increases in blood Pb from 1.0 µg/dL to 6.7 µg/dL (i.e., from the 10th to 90th percentile) were associated with significant increases in all-cause mortality, CVD mortality, and ischemic heart disease mortality. Exhibit 8 shows the adjusted HRs for these increases and all types of mortality, as well as population attributable fractions and avoidable deaths assuming a decrease in Pb to 1.0 µg/dL.

Exhibit 8. **Adjusted Hazard Ratios, Population Attributable Fractions, and Avoidable Deaths Associated with Pb Exposures (Lanphear et al., 2018)**

Type of Mortality	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Population Attributable Fraction (95% CI)	Avoidable Deaths (95% CI)
All-cause mortality	3.79 (3.18-4.50)	1.37 (1.17-1.60)	18.0% (10.9-26.1)	412,000 (250,000-598,000)
CVD mortality	4.44 (3.47-5.68)	1.70 (1.30-2.22)	28.7% (15.5-39.5)	256,00 (138,00-352,000)
Ischemic heart disease mortality	5.31 (4.06-6.93)	2.08 (1.52-2.85)	37.5% (23.4-48.6)	185,000 (116,00-241,000)
Source: Lanphear et al. (2018, Table 2)				

The cubic spline analyses indicated that the adjusted HRs for all types of mortality were steeper at lower concentrations of Pb than higher concentrations, as shown below in Exhibit 9.

Exhibit 9.   Dose-Response Curves for Concentrations of Pb in Blood and Mortality (Lanphear et al., 2018)
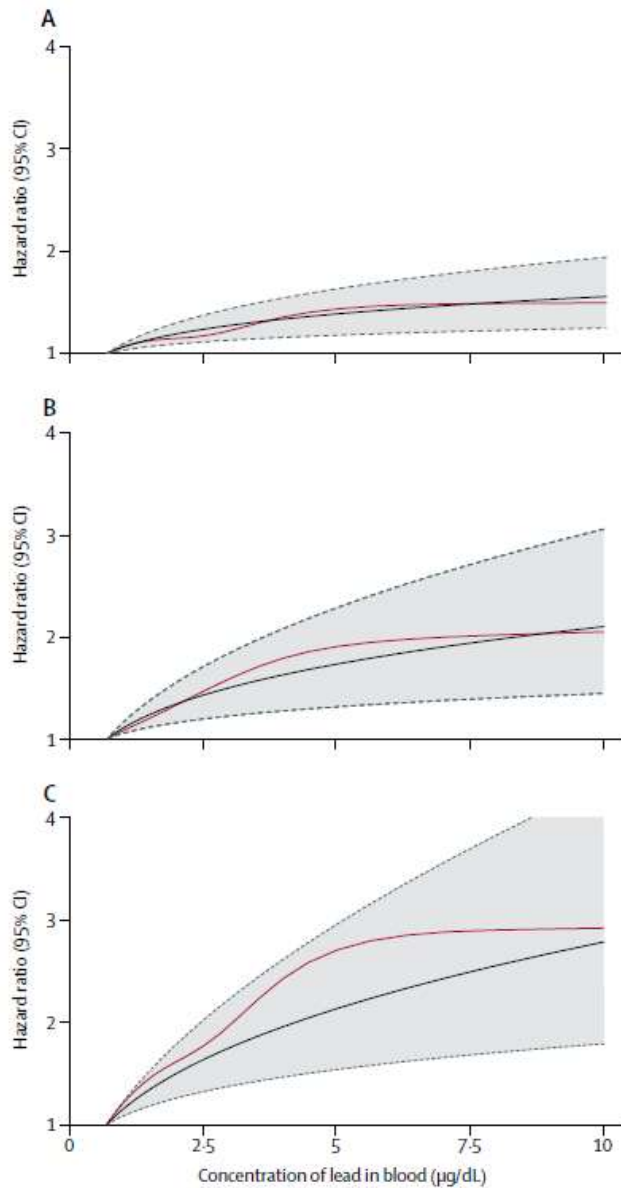
Adjusted hazard ratios (black lines) with 95% CIs (hatched lines) and restricted cubic spline (red lines) for (A) all-cause mortality, (B) cardiovascular disease mortality, and (C) ischemic heart disease mortality. Source: Lanphear et al. (2018, Figure 1)

When the analysis was restricted to participants with blood Pb levels below 5 µg/dL, the HR for CVD mortality was 1.95 (95% CI = 1.46-2.60).

3.2.4   Menke et al. (2006)

In their study *Blood Lead Below 0.48 μmol/L (10 μg/dL) and Mortality Among US Adults,* Menke et al. (2006) 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. The authors included 13,946 participants 20 years of age and older. 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. For CVD mortality, the authors used ICD-9 codes 390 to 434 and 436 to 459 and ICD-10 codes I00-I99. Mortality follow-up was approximately 12 years. 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 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. Baseline confounders were calculated for each tertile after standardizing to the U.S. population by age, sex and race-ethnicity. 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. The authors constructed three models to adjust for various potential confounders. In the first model, adjustment was made only for age, sex, and race-ethnicity. Additional potential confounders of the association between Pb and CVD mortality were added in Model 2 (see Exhibit 10 for list). In the final model, Menke et al. (2006) additionally adjusted for hypertension and kidney function, which are potential intermediates in the causal pathway for the association.

Exhibit 10 displays results of the analysis for all-cause, cardiovascular disease, and myocardial infarction mortality. When comparing the second (middle) tertile to the first tertile, a slight increase in CVD mortality was observed. When comparing the third tertile to the first tertile, a larger and statistically significant increase in risk was found. 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 10.   Hazard Ratios and 95% Confidence Intervals of All-Cause, CVD, and Myocardial Infarction 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

Note: Sample sizes (n) refer to the number of events.
* 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.
Source: Menke et al. (2006, Table 2).

Tests for linear trend across tertiles of blood Pb were computed by including tertile of Pb as a 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 10 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 11). This analysis revealed that the increase in all-cause and myocardial infarction occurred at blood Pb levels > 2.0 µg/dL. Stroke increased monotonically at all blood Pb levels included in the spline analysis (1 to 10 µg/dL). Spline results were not presented for CVD.

In a third analysis, due to the skewedness 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-fold 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,[7] 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 12.

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 12.

---

[7] 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 11.   Multivariate Adjusted Relative Hazard of Mortality Associated with Blood Pb Levels between 0.05 µmol/L (1 µg/dL) and 0.48 µmol/L (10 µg/dL) (Menke et al., 2006)
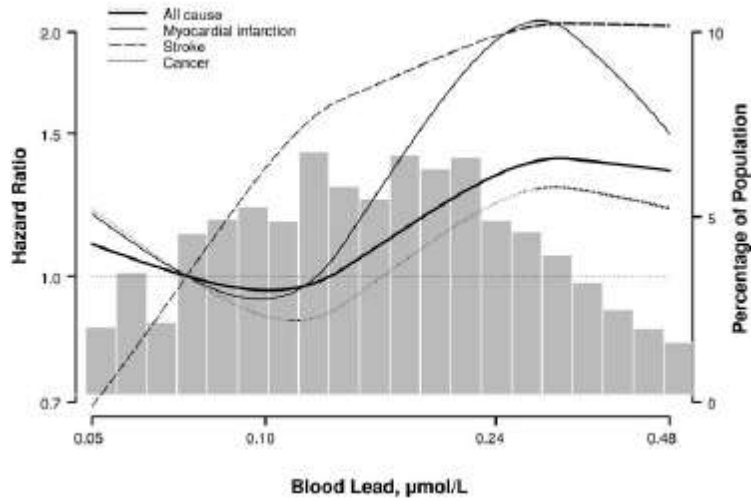
Note: Histogram of blood Pb levels is superimposed in the background and displayed on the right axis.
Source: Menke et al. (2006, Figure 2).

Exhibit 12.   Multivariate Adjusted Relative Hazards[1] of All-Cause and CVD Mortality (Menke et al., 2006)

Subgroup	HR of All-Cause Mortality (95% CI)	HR of CVD 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 12 are based on a continuous function. 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.

3.2.5   Ruiz-Hernandez et al. (2017)

In their paper *Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population,* Ruiz-Hernandez et al. (2017) aimed to evaluate how changes in blood Pb and cadmium exposures in the US population contribute to the changes in rates of CVD mortality between 1988-1994 and 1999-2004, after controlling for established cardiovascular risk factors. Participants in NHANES were included in the study (n = 21,418) if they were aged 40 years old or older and had complete data on Pb, cadmium, and other CVD risk factors. Mortality outcomes were determined using National Death Index records and ICD codes for CVD mortality (ICD-10 codes 100-178) and coronary heart disease (ICD-10 codes 120-125). To ensure that the same length of follow-up was used for both cohorts, participants in NHANES 1988-1994 and in NHANES 1999-2004 were followed through December 31st 1996 and December 31st 2006, respectively. The authors used weighting techniques to adjust NHANES data to be representative of the US population.

To calculate mortality rate ratios associated with a two-fold increase in blood Pb, Ruiz-Hernandez et al. (2017) estimated Poisson regression models for individual mortality data on log-transformed metal concentrations, which were adjusted for age at follow-up, sex, race, survey period and traditional CVD risk factors. These risk factors were: baseline smoking status, physical inactivity, obesity, hypertension, diabetes, high total cholesterol, low HDL cholesterol and lipid-lowering medication. Ruiz-Hernandez et al. (2017) additionally conducted analyses including interaction terms for age, smoking status, and survey period. The authors additionally used three approaches to examine mediation of CVD mortality by exposures to Pb and cadmium: the causal inference mediation approach, the difference in coefficients approach and the product of coefficients method. For all approaches, three models with varying levels of adjustment were used. In the first model, only age, race, and sex were adjusted for; CVD risk factors and cadmium levels were added in turn to all previous confounders in the second and third models, respectively. Results of the mediation analyses were absolute decreases in deaths attributable to decreases in Pb and cadmium exposures, and the percentage of total deaths attributable to these decreases in exposures.

After adjusting for differences in age, sex, race and risk factors between the two NHANES cohorts, Ruiz-Hernandez et al. (2017) found that further adjustment for blood Pb levels explained 25.4% of the observed decrease in CVD mortality rates from 1988-1994 to 1999-2004. Decreases in Pb exposures were associated with 51.9 avoided deaths per 100,000 person-years. Similar patterns were observed for coronary heart disease mortality. Results were consistent across methods, and in sensitivity analyses when using different methods to adjust for CVD mortality. Exhibit 13 displays the rate ratios for cardiovascular and coronary heart disease mortality associated with a doubling of blood Pb.

Exhibit 13. Rate Ratios for Cardiovascular and Coronary Heart Disease Mortality Associated with a Two-Fold Increase in Baseline Blood Pb

	Cardiovascular Disease		Coronary Heart Disease	
	Mortality rate ratio (95% CI)	*P* for interaction	Mortality rate ratio (95% CI)	*P* for interaction
Overall	1.19 (1.07, 1.31)	-	1.24 (1.10, 1.41)	-
Sex				
Men	1.09 (0.95, 1.25)	0.07	1.14 (0.98, 1.33)	0.11
Women	1.31 (1.13, 1.52)		1.44 (1.14, 1.82)	
Smoking				
Never	1.35 (1.14, 1.59)	0.07	1.63 (1.32, 2.01)	0.003
Ever	1.10 (0.96, 1.25)		1.10 (0.95, 1.28)	
Survey				
1988-94	1.17 (1.04, 1.31)	0.47	1.25 (1.10, 1.42)	0.77
1999-2004	1.26 (1.05, 1.50)		1.20 (0.88, 1.62)	
Source: Ruiz-Hernandez et al. (2017, Table 1)				

3.2.6   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 the paper. Participants were followed through December 31, 2000. Using the National Death Index and the International Classification of Disease (Tenth Revision), Schober et al. identified deaths due to malignant neoplasms (ICD-10 codes C00-C97) and major CVD (ICD-10 codes I00-I78). The median length of follow-up was 8.55 years, during which there were 2,515 deaths.

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 (defined as the participant's age at the baseline examination) 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, thereby 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. Further, Schober et al. (2006) stated that because the cancer mortality and blood Pb relationship was different for men 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. (2006) 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 blood Pb concentrations as a continuous variable. All multivariate models were adjusted for sex, race/ethnicity, education level, and smoking status. The authors also analyzed alcohol intake, census region, and urban status as potential confounders; however, these variables were ultimately not included in the model because they were judged not very predictive of mortality and did not alter the direction of the Pb-mortality relationship. Similarly, none of the interaction terms between Pb and the selected covariates were included in the model for these reasons.

The number of deaths and multivariate-adjusted relative risks of mortality due to all causes, CVD, and cancer are presented in Exhibit 14. There were a total of 2,485 deaths from all causes, 1,189 from CVD, and 543 from cancer. 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.

Exhibit 14. 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).

3.2.7 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*[8] 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 (NAS), 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 identify deaths, the study authors sent birthday cards and supplemental questionnaires to study participants. Next of kin or postal authorities

---

[8] Note: the original study was published in 2009 but this summary is based on the correction to the study which was posted to *Circulation* in 2014 (Weisskopf et al., 2014). The EPA ISA and the NTP monograph both reviewed the uncorrected version of this study.

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 through March 2007. Cause-specific mortalities were classified using ICD-9 codes 390 to 459.

In the statistical analysis, the study authors first 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). Multivariate regression models were adjusted for age, smoking, and education. The authors investigated additional covariates (alcohol, BMI, physical activity, cholesterol, serum HDL, diabetes, race and hypertension), but opted not to include these covariates in the final models. For each mortality endpoint, analyses were performed with and without inclusion of individuals who had pre-existing diseases associated with the endpoint at baseline (e.g., CVD in the CVD mortality model). 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. All analyses were conducted separately for blood Pb and bone (patella and tibia) Pb levels.

Weisskopf et al. (2009) did not find any statistically significant associations between blood or bone Pb and any endpoint evaluated. The results of the blood Pb analyses are summarized in Exhibit 15. In spline regression models presented by Weisskopf et al. (2009), there was some suggestion that the association with all-cause mortality, all cardiovascular disease and ischemic heart disease related mortality plateaus at higher bone Pb concentrations, although the authors note that in these ranges the data were sparse and the confidence intervals were wide.

Exhibit 15.   Hazard Ratios and 95% Confidence Intervals for All-Cause, CVD, Ischemic Heart Disease, and Other Cardiovascular Mortality by Category of Blood Pb at Baseline (Weisskopf et al., 2009)

	Tertile of Blood Pb			
	1 (<4 µg/dL)	2 (4 to 6 µg/dL)	3 (>6 µg/dL)	*p* for trend
N	320	561	354	
Follow-up, y	2472	4431	2867	
All-Cause Mortality				
Deaths	72	144	110	
Crude	Reference	1.11 (0.84-1.47)	1.27 (0.94-1.71)	0.11
Multivariable 1[a]	Reference	0.81 (0.53-1.25)	0.93 (0.59-1.45)	0.84
Multivariable 2[b]	Reference	0.69 (0.41-1.19)	0.84 (0.50-1.42)	0.67
All Cardiovascular Mortality				
Deaths	38	84	63	
Crude	Reference	1.23 (0.84–1.80)	1.40 (0.94–2.09)	0.10
Multivariable 1[a]	Reference	0.86 (0.49–1.51)	0.99 (0.55–1.78)	0.96
Multivariable 2[b]	Reference	0.63 (0.29–1.38)	0.69 (0.33–1.47)	0.44
Ischemic Heart Disease (Subset of All Cardiovascular)				
Deaths	17	36	29	
Crude	Reference	1.19 (0.67–2.11)	1.44 (0.79–2.61)	0.23
Multivariable 1[a]	Reference	1.13 (0.49–2.62)	1.30 (0.54–3.17)	0.55
Multivariable 2[b]	Reference	1.02 (0.32–3.21)	1.04 (0.33–3.22)	0.95
Other Cardiovascular (Subset of All Cardiovascular)				
Deaths	28	57	40	
Crude	Reference	1.26 (0.76–2.11)	1.37 (0.80–2.36)	0.27
Multivariable 1[a]	Reference	0.64 (0.28–1.46)	0.77 (0.34–1.74)	0.65
Multivariable 2[b]	Reference	0.30 (0.09–1.03)	0.39 (0.12–1.23)	0.23
[a] Adjusted for age at XRF, smoking (never/former/current and pack years), and education. [b] Same model but excluding the 154 participants (53 deaths) who had heart disease (146) or stroke (11) at bone Pb measurement. Source: Weisskopf et al. (2009, Table 3)				

The authors hypothesized that their results vary from the Schober et al. (2016) and Menke et al. (2016) results due to a smaller sample size (i.e., not enough power to detect a relationship) or potentially due to greater variability in Pb exposure in the Greater Boston area. The variability could affect 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). Additionally, the individuals in the NAS cohort are

older than those in the Menke et al. (2006) and Schober et al. (2006) papers. 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. An additional explanation for the difference in the findings of Weisskopf compared to Menke or Schober is an issue with selection bias and conditioning on an intermediate (often referred to as "overadjustment", see Appendix A: Discussion of Møller and Kristensen (1992) and Weisskopf et al. (2009) for details) in the NAS cohort and Pb sub-study. This was specifically addressed in a subsequent publication (Weisskopf, Sparrow, Hu, & Power, 2015), summarized below.

3.2.8   Weisskopf et al. (2015)

Weisskopf et al. (2015) explores the idea that studies of environmental toxicant exposures are susceptible to collider stratification bias (hereafter referred to as "selection bias") or bias from conditioning on an intermediate (often referred to as "over adjustment").

These two types of biases are explained by Weisskopf et al. (2015) as follows:

> Given the routes of [Pb] exposure and cumulative nature of bone [Pb] measurements, measured bone [Pb] may include, and is almost certainly correlated with [Pb] exposures prior to cohort formation. Therefore, it is reasonable to think that (1) unique prior correlates of [Pb] exposure and mortality both influence study participation at both study inception and recruitment into the lead sub-study, resulting in [selection bias] in the absence of analytical methods to mitigate this bias, an (2) [Pb] exposure-related health effects may influence study participation in both the original study and the [Pb] sub study, resulting in bias from conditioning on an intermediate of the [Pb] exposure-mortality association. (p. 7)

That is, individuals may be excluded at the cohort inception, and at the later point of the Pb sub-study, due to cohort formation criteria such as an absence of prior CVD, which will skew the cohort toward heart healthy individuals. Additionally, individuals may not be able to participate in a study due to illness associated with previous Pb exposure, resulting in an underestimate of the relationship between Pb and the adverse health outcome.

To explore this idea, Weisskopf et al. (2015) implemented several methods to mitigate bias in their analysis of blood, patella and tibia Pb association with mortality due to ischemic heart disease, CVD and all-causes, which were presented in a previous publication (Weisskopf et al., 2009). We focus our discussion here on the CVD mortality findings.

Weisskopf et al. (2015) developed a base model exploring the relationship between patella Pb and ischemic heart disease, CVD and all-cause related mortality. This model is similar to the Weisskopf et al. (2009) model with a slightly different base population, cut points for the tertiles and confounders (see Model 1 in Exhibit 16). No statistically significant relationship was noted from this base model. To partially adjust for potential selection bias, Weisskopf et al. (2015) developed Model 2, which adjusted for additional indicators of socioeconomic status (SES) given that SES is correlated with Pb exposure and study participation. However, as displayed in Exhibit 16, this did not change the non-significant findings for patella Pb as it relates to mortality. Similar results were observed for tibia Pb and blood Pb.

Weisskopf et al. (2015) noted that the eligibility criteria for the Normative Aging Study (NAS) may also introduce potential selection bias. Specifically, in order to be entered into the cohort, an individual could not have prior CVD or other risk factors for CVD such as high blood pressure or past treatment for hypertension. For older individuals this creates a strong selection bias toward heart-healthy people (Weisskopf et al., 2015). That is, individuals who may be more susceptible to the effects of Pb exposure may not have been eligible to enter the cohort when it originated due to existing CVD or risk factors for CVD. To mitigate the issue of selection bias introduced by the NAS eligibility criteria, Weisskopf et al. (2015) reanalyzed the data from the NAS cohort by restricting the analysis to individuals less than 45 years of age at entry into the cohort, i.e., individuals less likely to experience CVD. In this reanalysis, a statistically significant association was found between CVD mortality and patella Pb in the highest tertile as compared to the lowest tertile (Weisskopf et al., 2015). Additionally, Weisskopf et al. (2015) found a statistically significant trend in regards to increasing patella Pb levels and increased risk of death from CVD after these adjustments (see Model 3 in Exhibit 16). No significant associations with CVD mortality were observed for tibia Pb or blood Pb.

Additionally, to eliminate some bias as a result of non-participation in the Pb sub-study (which occurred after entry into the NAS cohort) due to Pb-exposure related health effects, the authors implemented inverse probability weighting (IPW). That is, using data available on NAS participants with and without bone Pb measurements (taken with a k-shell x-ray fluorescence machine (K-XRF)), Weisskopf et al. (2015) weighted the Pb sub-study population to make it representative of all who were alive at the time of the KXRF sub-study. This addresses the fact that health status is a known predictor of study participation and loss to follow-up (i.e., individuals that entered the NAS but became ill as a result of Pb exposure may have been less likely to enter the Pb sub-study). IPW allows the population to be weighted to account for this loss to follow-up for the Pb sub-study. It is important to note that IPW cannot be implemented to address non-participation at cohort formation, because there are no data on those who did not participate in the NAS.

Using an IPW population for the Pb sub-study that was restricted to individuals of 45 years old or younger at the origination of the NAS cohort, Weisskopf et al. (2015) found an even stronger trend relating increasing patella Pb levels to CVD related mortality (see Model 4 in Exhibit 16). In the models relating tibia Pb and blood Pb to CVD mortality, no significant associations were observed.

Exhibit 16. **Adjusted Hazard Ratios (HR: 95% CI) for All-Cause, Cardiovascular Disease and Ischemic Heart Disease Mortality, by Tertile[a] of Patella Pb at Baseline in All NAS Participants and Those <45 Years Old (Weisskopf et al., 2015)**

Health Effect	Deaths	Tertile of patella Pb			p-trend
		1st <20 µg/g	2nd 20-31 µg/g	3rd > 31 µg/g	
Model 1: Base Model[b] (N=835)					
All-Cause Mortality	235	Ref	1.23 (0.82-1.85)	1.34 (0.90-2.00)	0.16
All Cardiovascular Mortality	134	Ref	1.22 (0.71-2.10)	1.46 (0.86-2.48)	0.15
Ischemic Heart Disease Mortality	61	Ref	1.73 (0.74-4.07)	2.01 (0.86-4.68)	0.12
Model 2: Additional SES Adjustment[c] (N=835)					
All-Cause Mortality	235	Ref	1.16 (0.76-1.79)	1.25 (0.83-1.90)	0.30
All Cardiovascular Mortality	134	Ref	1.16 (0.65-2.08)	1.45 (0.83-2.53)	0.16
Ischemic Heart Disease Mortality	61	Ref	1.96 (0.79-4.88)	2.11 (0.87-5.13)	0.13
Model 3: Additional SES Adjustment[c] and Restriction to 45 Years Old or Younger at NAS Inception (n=637)					
All-Cause Mortality	135	Ref	1.30 (0.75-2.26)	1.72 (0.98-3.03)	0.05
All Cardiovascular Mortality	75	Ref	1.36 (0.63-2.90)	2.23 (1.02-4.84)	0.03
Ischemic Heart Disease Mortality	35	Ref	2.74 (0.78 – 9.63)	4.60 (1.26-16.8)	0.02
Model 4: Additional SES Adjustment[c], Restriction to 45 Years Old or Younger at NAS Inception, and IPW (n=637)					
All-Cause Mortality	135	Ref	1.41 (0.86-2.30)	1.86 (1.12-3.09)	0.02
All Cardiovascular Mortality	**75**	**Ref**	**1.53 (0.78-2.99)**	**2.47 (1.23-4.96)**	**0.009**
Ischemic Heart Disease Mortality	35	Ref	3.09 (1.01-9.46)	5.20 (1.61-16.8)	0.005

[a] Tertiles of patella Pb are based on the distribution among NAS participants 45 years old or younger at NAS entry
[b] Adjusted for age at KXRF, age at KXRF squared, smoking (never/former/current & pack-years), and education
[c] Additionally adjusted for occupation and salary at NAS entry, mother's education and occupation, father's education and occupation
Source: Weisskopf et al. (2015, Table 2)

Using the fully adjusted model (i.e., additional SES adjustments, IPW weighted and restricted to 45 years of age or younger at cohort formation) to explore the continuous relationship between

patella Pb and CVD, Weisskopf et al. (2015) implemented a spline regression analysis (see Exhibit 17). Their analysis found that the nonlinear components of their model were non-significant, implying the relationship is indeed linear.

Exhibit 17.   Flexible Spline Model between Patella Bone Pb Concentration and the log HR for Cardiovascular Related Mortality
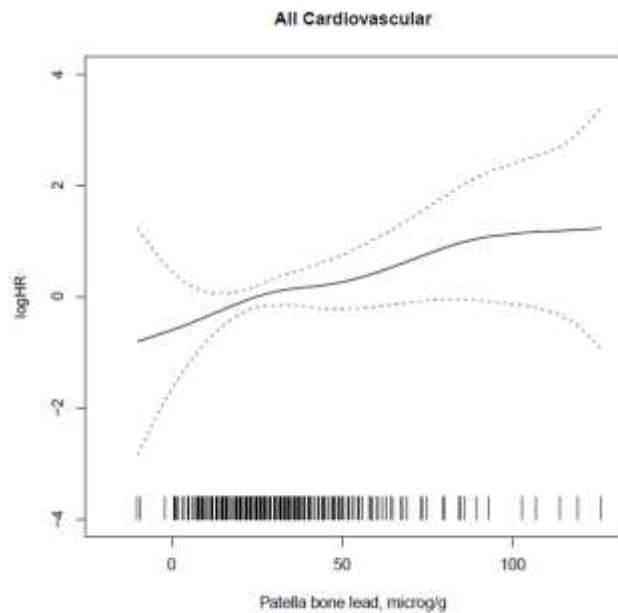
Adjusted for age at KXRF, age at KXRF squared, smoking (never/former/current and packyears), and education among white men 45 years old or younger at NAS entry (n=637) with IPW.
P value for non-linear component =0.91
Source: Weisskopf et al. (2015, Supplemental Material Figure S2)

Weisskopf et al. (2015) explain that the lack of finding with tibia bone Pb may imply that it is "the re-release of [Pb] from bone at older ages that is most relevant for cardiovascular mortality than cumulative past exposure at earlier ages" (p. 24). This conclusion is based on the fact that the Pb in the patella (composed mainly of trabecular bone) is more mobile than the Pb in the tibia (composed mainly of cortical bone), with a half-life of just a few years compared to potentially decades (U.S. EPA, 2013b). Therefore, tibia Pb is less likely to be re-released to the body compared to patella Pb.

According to Weisskopf et al. (2015) the lack of association with blood Pb "suggests that the time window of relevance for the effect of Pb re-released from bone is still a longer-term one since the half-life of Pb in blood is on the order of a month while that of Pb in the patella is on the order of years." (p. 28) However, this statement is made while recognizing the fact that prior studies, such as Menke et al. (2006) and Schober et al. (2006), have found a relationship between blood Pb and CVD mortality. We hypothesize that this difference in findings may be

related to differences in the populations assessed or functional form used to describe the relationship between Pb exposure and CVD mortality risk. For example, the average blood Pb levels for the Weisskopf cohort (5.5 µg/dL for individuals less than 45 years of age at cohort formation[9]) is higher than the average blood Pb level in the Schober (4.14 µg/dL) and Menke (2.58 µg/dL) cohorts. Further, the Weisskopf et al. (2015) cohort is composed of only older white males whereas the other cohorts evaluated are more diverse. Additionally, Weisskopf et al. (2015) hypothesized that the difference may be "because of more variability in [Pb] exposure in the Boston, MA area resulting in worse correlation with bone Pb in the NAS group compared to NHANES" (p. 24). Additionally, the sample size of the Weisskopf study is 835. This sample size is smaller than that of the Menke et al., (2006) study which used a NHANES cohort of 13,946 men and women of multiple races. The smaller sample size results in less statistical power.

Additionally, Menke and Schober also assumed the relationship between CVD mortality risk and Pb exposure was of the log-log form whereas Weisskopf et al. (2015) assumed the relationship to be log-linear. Given the higher blood Pb concentrations in the Weisskopf cohort, and the potential for the true relationship to be log-log , it is possible that because of the higher blood Pb levels in this cohort it was harder to detect an association with blood Pb given the smaller magnitude of an effect for a unit change in blood Pb levels.

---

[9] Data provided by study author via email on March 6, 2016.

4. Derivation of the Concentration Response Function

This chapter describes the process of selecting the key study (or studies) from which we derive the concentration-response function. In Section 4.1 we present our methodology and additional criteria for selecting a key study or studies from which to develop a concentration-response function. Section 4.2 describes our methods for deriving a concentration-response function from our key studies. An example application of our concentration-response function is presented in Section 4.3.

4.1 Selection of Key Study/Studies

In considering the remaining eight studies that examined the relationship between blood Pb and CVD mortality in U.S. adults, we used additional criteria to determine which study or studies may be most useful for developing a concentration-response function that would be most applicable and useful for benefits analysis for a current day U.S. population. Specifically, we further narrowed down the potential key studies using the following criteria:

- The study is representative of the general U.S. population, as characterized by:

    - Mean blood Pb level below 5 µg/dL,

    - Relatively large sample size

- The study included an analysis of CVD mortality with blood Pb as a continuous, rather than categorical, variable.

Exhibit 18 indicates which studies were selected for further analysis for deriving the concentration response function. Four studies remained for potential analysis after applying our criteria to select a key study: Menke et al. (2006), Aoki et al. (2016), Ruiz-Hernandez et al. (2017) and Lanphear et al. (2018). The Schober et al. (2006) paper also had a population with blood Pb levels less than 5 µg/dL and was based on a generalizable U.S. population survey. However, we were unable to obtain a continuous concentration-response function for this study.[10] A side-by-side comparison of our four potential key studies is provided in Exhibit 2019.

---

[10] We contacted Dr. Schober and her co-author, Dr. Mirel, to inquire whether there was a continuous concentration-response function available for the association between Pb and CVD mortality. Although the authors were willing to assist, it was not feasible to reanalyze the data.

Exhibit 18.   Application of Initial Exclusion Criteria to Potential Key Studies

Study	Population	Mean Blood Pb Level Less Than 5 µg/dL?	Blood Pb Analyzed as a Continuous Variable with CVD Mortality Risk	Key Finding	Selected for Further Evaluation?
Aoki et al. (2016) *Blood lead and other metal biomarkers as risk factors for cardiovascular disease mortality*	>18,600 adults aged 40 years of age and older from NHANES 1999-2010	**Yes.** 1.73 µg/dL	**Yes**	HR for CVD mortality = 1.44 (95%CI: 1.05-1.98) for a 10-fold increase in hematocrit-corrected blood Pb	**Yes.**
Khalil et al. (2009) *Association of blood lead concentrations with mortality in older women: a prospective cohort study*	533 white women aged 65–87 enrolled either at the University of Pittsburgh or University of Maryland	**No.** 5.3 ± 2.3 µg/dL	**No**	HR for CVD mortality is 1.78 (95% CI: 0.92, 3.45) in the high Pb group (>8 µg/dL) compared to low Pb group (<8 µg/dL)	**No.** Average blood Pb > 5 µg/dL. Analysis based on continuous blood Pb measure not available.
Lanphear et al. (2018) *Low-level lead exposure and mortality in US adults: a population-based cohort study*	>14,200 adults aged 20 years and older with no cut off level for blood Pb NHANES III (1988-1994) (Note: additional analyses performed on >10,600 adults aged 20 and older with blood Pb <5 µg/dL)	**Yes.** 2.71 ± 0.13 µg/dL	**Yes.**	All participants: HR for CVD mortality is 1.70 (1.30-2.22) for a 6.7-fold increase in blood Pb Participants with blood Pb <5 µg/dL: HR for CVD mortality is 1.95 (1.46-2.60) for a 5-fold increase in blood Pb	**Yes.**

Study	Population	Mean Blood Pb Level Less Than 5 µg/dL?	Blood Pb Analyzed as a Continuous Variable with CVD Mortality Risk	Key Finding	Selected for Further Evaluation?
Menke et al. (2006) *Blood lead below 0.48 µmol/l (10 µg/dL) and mortality among US adults*	>13,900 adults aged 20 years and older from NHANES III (1988-1994)	**Yes.** 2.58 µg/dL	**Yes**	HR for CVD mortality is 1.53 (1.21-1.94) for a 3.4-fold increase in blood Pb levels or the difference between the logged 80th (4.92 µg/dL) and 20th (1.46 µg/dL) percentiles	**Yes.**
Ruiz-Hernandez et al. (2017) *Declining exposures to lead and cadmium contribute to explaining the reduction in cardiovascular mortality in the US population, 1988-2004*	>15,400 adults aged 40 years and older with no cut off for blood Pb NHANES III (1988-1994) and NHANES (1999-2004)	**Yes.** NHANES III: 3.2 µg/dL 1999-2004: 1.9 µg/dL	**Yes**	HR for CVD mortality is 1.19 (1.07-1.31) for a doubling of log transformed blood Pb	**Yes.**
Schober et al. (2006) *Blood lead levels and death from all causes, CVD, and cancer: results from the NHANES III mortality study*	9,686 participants in NHANES III (1988-1994) who were 40 years of age or older	4.14[a]	**No**	HR for CVD related mortality 1.55 (95% CI: 1.16-2.07) when comparing individuals with blood Pb <5 µg/dL to those with blood Pb >10 µg/dL	**No.** Analysis based on continuous blood Pb measure not available.

Study	Population	Mean Blood Pb Level Less Than 5 µg/dL?	Blood Pb Analyzed as a Continuous Variable with CVD Mortality Risk	Key Finding	Selected for Further Evaluation?
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*	860 men in the Normative Aging Study	5.6 µg/dL	**No**[11]	No statistically significant relationship found between blood or bone Pb and CVD mortality.	**No.** Mean blood Pb greater than 5 µg/dL.
Weisskopf et al. (2015) *Biased exposure–health effect estimates from selection in cohort studies: are environmental studies at particular risk?*	637 men in the Normative Aging Study, ≤45 years old at study inception	5.5 µg/dL	**Yes**. Spline analysis conducted but not quantitative description of relationship	No statistically significant relationship found between blood Pb and CVD mortality. Increased risk of CVD mortality was found with increased patella Pb after adjustment for potential selection bias.	**No.** Mean blood Pb level >5 µg/dL.

BMD = bone mineral density; BMI = body-mass index; CI = confidence ratio; CVD = cardiovascular disease; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; XRF = x-ray fluorescence

a 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).

---

[11] After contacting the authors, Dr. Weisskopf was able to provide this information, but it is not described here due to the fact that the study was excluded for other reasons.

Exhibit 19. **Side-by-Side Comparison of Potential Key Studies for Use in Developing a Concentration-Response Function**

Attribute of Interest	Menke et al. (2006) *Blood Lead below 0.48 µmol/l (10 µg/dL) and Mortality among U.S. Adults*	Aoki et al. (2016) *Blood Lead and Other Metal Biomarkers as Risk Factors for CVD Mortality*	Ruiz-Hernandez et al. (2017) *Declining exposure to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004*	Lanphear et al. (2018) *Low-level lead exposure and mortality in US adults: a population-based cohort study*
Dataset	NHANES III	NHANES 1999-2010	NHANES III and NHANES 1999-2004	NHANES III
Year of Blood Pb Collection	1988-1994	1999-2010	1988-1994 and 1999-2004	1988-1994
Sample Size and Population	>13,900 adults aged 20 years and older with blood Pb < 10 µg/dL	>18,600 adults aged 40 years of age and older with no cutoff for blood Pb level	>15,400 adults aged 40 years and older with no cut off for blood Pb	All participants: >14,200 adults aged 20 years and older with no cut off level for blood Pb Participants with blood Pb <5 µg/dL only: >10,600 adults aged 20 and older
Number of CVD related Deaths	766	985	890	All participants: 1,801 Participants with blood Pb <5 µg/dL only: Not reported
Geometric Mean Pb (SE)	2.58 µg/dL (not given)	1.73 µg/dL (0.02)	NHANES III: 3.2 µg/dL (SE not given) NHANES 1999-2004: 1.9 µg/dL (SE not given)	All participants: 2.71 µg/dL (0.131) Blood Pb <5 µg/dL only: Not reported

Exhibit 19.   Side-by-Side Comparison of Potential Key Studies for Use in Developing a Concentration-Response Function

Attribute of Interest	Menke et al. (2006) *Blood Lead below 0.48 µmol/l (10 µg/dL) and Mortality among U.S. Adults*	Aoki et al. (2016) *Blood Lead and Other Metal Biomarkers as Risk Factors for CVD Mortality*	Ruiz-Hernandez et al. (2017) *Declining exposure to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004*	Lanphear et al. (2018) *Low-level lead exposure and mortality in US adults: a population-based cohort study*
Participant Age: Arithmetic Mean (SE)	44.4 (0.5)	57.5 (0.2)	Not given	All participants: 44.1 (not reported) Blood Pb <5 µg/dL only: Not reported
Pb Biomarker	Whole blood Pb	Hematocrit-corrected blood Pb	Whole blood Pb	Whole blood Pb
Key Finding	Hazard ratio (95% CI) of 1.53 (1.21-1.94) for a 3.4-fold increase in blood Pb	Hazard ratio (95% CI) of 1.44 (1.05–1.98) for a 10-fold increase hematocrit-corrected blood Pb	Mortality rate ratio (95% CI) of 1.19 (1.07-1.31) for a doubling of blood Pb	All participants: Hazard ratio (95% CI) of 1.70 (1.30-2.22) for a 6.7-fold increase in blood Pb Blood Pb <5 µg/dL only: Hazard ratio (95% CI) of 1.95 (1.56-2.60) for a 5-fold increase in blood Pb
ICD Codes for CVD	ICD-9 = 390-434, 436-459; ICD-10 = I00-I99	ICD-10 = I00-I99	ICD-10 = I00-I78	ICD-9 = 390-459; ICD-10 = I00-I99

Exhibit 19.   Side-by-Side Comparison of Potential Key Studies for Use in Developing a Concentration-Response Function

Attribute of Interest	Menke et al. (2006) *Blood Lead below 0.48 µmol/l (10 µg/dL) and Mortality among U.S. Adults*	Aoki et al. (2016) *Blood Lead and Other Metal Biomarkers as Risk Factors for CVD Mortality*	Ruiz-Hernandez et al. (2017) *Declining exposure to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004*	Lanphear et al. (2018) *Low-level lead exposure and mortality in US adults: a population-based cohort study*
Confounders Considered in Key Analysis	Age, race/ethnicity, sex, smoking status, education, alcohol consumption, CRP, physical activity, low income, total cholesterol, urban residence, post-menopausal status, hypertension, level of kidney function, diabetes mellitus, body mass index	Race, Hispanic origin, sex, smoking status, education, alcohol intake, CRP, blood cadmium, serum iron, serum calcium[1]	Age, sex, race, smoking status, physical inactivity, obesity, hypertension, diabetes, high total cholesterol, low HDL cholesterol, lipid-lowering medication, survey period, and log-transformed cadmium	Age, sex, household income, ethnic origin, body mass index, smoking status, hypertension, urinary cadmium, alcohol consumption, physical activity in previous month, healthy eating index, serum cholesterol, and glycated hemoglobin
Limit of Detection	1.0 µg/dL	0.25-0.3 µg/dL	NHANES III: 1.0 µg/dL NHANES 1999-2004: 0.25-0.3 µg/dL	1.0 µg/dL
Maximum Length of Follow-Up	13 years	13 years	8-9 years	24 years
Dates of Follow-Up	Through December 31, 2000	Through December 31, 2011	NHANES III: Through December 31, 1996 NHANES 1999-2004: Through December 31, 2006	Through December 31, 2011

[1] Age was accounted for by use as the time scale in the Cox proportional hazard regression analyses.

After comparing our four remaining potential key studies, we opted to include all of them for use in developing a concentration-response function. As shown in Exhibit 19, all of these studies are large, population-based studies that analyze NHANES data and use the National Death Index database to identify cases of CVD mortality. NHANES is based on a nationally representative sample of individuals throughout the U.S. and uses a rigorous methodology that includes trained interviewers, standardized procedures, and quality control measures. Another advantage of the use of NHANES is the availability of detailed information on potential confounders. However, the possibility of residual confounding remains, and each study looked a slightly different set of potential confounders. The National Death Index is a comprehensive source for death records in the United States. Since all of the studies use this source, the potential for misclassification of CVD mortality cases is similar in each study. Limitations common to the methodology used in all of the studies (for example, the reliance on one baseline blood Pb measurement to characterize Pb exposures) are discussed in Sections 5 and 6.

Though all of the potential key studies are based on NHANES data, they do not all use the same NHANES cycle in their analyses. Menke et al. (2006) and Lanphear et al. (2018) both analyzed data from NHANES III. In this cycle of NHANES, blood Pb was measured during the years 1988-1994. Thus, blood Pb levels of participants are higher than would be expected given current exposures to Pb. The mean blood Pb levels in the Menke et al. (2006) and Lanphear et al. (2018) studies are 2.58 and 2.71 µg/dL, respectively. In contrast, the mean blood Pb level for individuals over the age of 40 from the 2013-2014 NHANES is estimated to be 1.17 µg/dL. The two remaining potential studies for selection, Aoki et al. (2016) and Ruiz-Hernandez et al. (2017), both included more recent NHANES data (1999-2010 and 1999-2004, respectively). Ruiz-Hernandez et al. (2017) analyzed participants from both NHANES III and NHANES 1999-2004, with mean blood Pb levels in each cohort of 3.2 and 1.9 µg/dL, respectively. Aoki et al. (2016) examined the lowest blood Pb levels, with a mean blood Pb level of 1.72 µg/dL; this study has blood Pb levels closest to current mean blood Pb levels in the U.S.

In addition to using the same NHANES cohort, the Menke et al. (2006) and Lanphear et al. (2018) papers present similar analyses. However, the Lanphear et al. (2018) study has advantages over the Menke et al. (2006) study. Firstly, since it is more recent, Lanphear et al. (2018) has the benefit of an additional 11 years of follow-up of participants in the National Death Index, and includes a larger number of deaths in the analysis. Additionally, the Lanphear et al. (2018) study has more extensive control for confounders. For example, the Lanphear et al. (2018) paper controlled for co-exposures to cadmium, which has also been associated with increases in CVD mortality in prior research, as well as a healthy eating index and glycated hemoglobin. Although the Lanphear et al. (2018) study is preferred for the aforementioned reasons, we opted to include both studies for comparison purposes. In addition to their analysis of all participants, Lanphear et al. (2018) present a hazard ratio based on participants with blood Pb levels <5 µg/dL only. Since these blood Pb levels are more in line with current levels of blood Pb exposures, we additionally include a concentration-response function based on the beta from this secondary analysis.

As previously stated, the Aoki et al. (2016) study examined the most recent NHANES data and thus is based on blood Pb levels that are more representative of current levels than those in the other studies. Additionally, the paper includes careful consideration of non-Pb biomarkers, as well as measurement error in blood Pb. The Aoki et al. (2016) paper is the only study to consider the effects of Pb on RBC concentration by correcting results for hematocrit levels. For these reasons, we also opted to select this study as a key study from which to develop a concentration-response function.

Since the Aoki et al. (2016) study presents numerous regression models, we must also select the most appropriate analyses from which to develop a concentration-response function. Based on the findings in the Aoki et al. (2016) study, the ideal model for use in benefits analysis would be one that corrects blood Pb for red blood cell concentration and includes the identified key confounding variables. That is, a model which includes demographic data (race/Hispanic origin and sex), smoking status (never, former and current), education (less than high school, high school, and college or higher), alcohol intake (number of drinks per week), blood cadmium and serum iron. Since serum calcium, c-reactive protein and BMD were not found to be operating as strong confounders in the model, these variables would not be included. Aoki et al. (2016) did not evaluate a model using this exact combination of confounders. However, given that the weak confounders have little impact on the hazard ratio in the fully adjusted model (model 1), we have selected the fully adjusted model for development of a concentration-response function. This model is also preferred because it uses the hematocrit correction, which is the more accurate correction to use as it represents the count of red blood cells directly.

The final potential key study identified in our search is the paper by Ruiz-Hernandez et al. (2017). As previously stated, this paper uses a combination of older (NHANES III) and more recent (1999-2004) NHANES data. Although the overall blood Pb level in the study is not stated, the blood Pb levels in participants from the 1999-2004 cohort (1.9 µg/dL) are more in line with current levels in U.S. adults. The study also had extensive control of confounders, including traditional risk factors for cardiovascular disease and co-exposures to cadmium. Thus, we also chose to include this study for further analysis.

To summarize, we selected analyses from studies by Menke et al. (2006), Aoki et al. (2016) (model A1), Ruiz-Hernandez et al. (2017), and Lanphear et al. (2018) (models with all participants and participants with blood Pb <5 µg/dL only) for use in developing concentration-response functions.

4.2   Concentration-Response Functions Derived from Key Studies

The four key studies – Menke et al. (2006), Aoki et al. (2016), Lanphear et al. (2018) and Ruiz-Hernandez et al. (2017) – all use regression models to relate log-transformed blood Pb levels to CVD mortality. The concentration-response function associated with the relationship between blood Pb and CVD mortality modeled in each study is:

$$\Delta CVD\ Mortality = \ y_1 \left(1 - e^{\beta \log_z \left(\frac{x_2}{x_1}\right)}\right)$$

(Equation 1)

Thus, the function necessary to estimate the number of cases associated with a change in blood Pb levels is:

$$Cases\ Avoided = \ y_1\left(1 - e^{\beta\, \log_z\left(\frac{x_2}{x_1}\right)}\right) * pop \qquad \text{(Equation 2)}$$

Where:

y_1 =   Baseline hazard rate of CVD mortality in baseline scenario (i.e., without the rule)

β =   Beta coefficient, which represents the change in CVD mortality per unit change in blood Pb

$\log_z$ =   Log transformation to the base z (e.g., $\log_{10}$)

x_2 =   Blood Pb level associated with the rule

x_1 =   Blood Pb level without the rule

pop =   Population for whom the change in blood Pb occurs

Equation 2 can be used to estimate the avoided CVD mortality from reductions in blood Pb. For example, it can be used to estimate the expected changes in CVD mortality associated with a rule or regulation to reduce blood Pb levels in a population.

The beta coefficient, β, varies based on the study in question and is calculated by:

$$\beta = \frac{\ln(Hazard\ ratio)}{\log_z(Fold\ increase\ in\ blood\ Pb\ for\ hazard\ ratio)} \qquad \text{(Equation 3)}$$

For example, the beta from Aoki et al. (2016) is based on a hazard ratio of 1.44, which was derived from a 10-fold increase in blood Pb levels. Thus, the beta coefficient is equal to $\ln(1.44)/\log_{10}(10)$, which is 0.36. Exhibit 20 displays the study-specific inputs for Equation 2 associated with each of our selected key studies.

Exhibit 20. Inputs to the Health Impact Function Based on Key Studies

Variable	Menke et al. (2006)	Aoki et al. (2016)	Ruiz-Hernandez et al. (2017)	Lanphear et al. (2018)	
				All Participants	Blood Pb <5 µg/dL
Log transformation ($\log_z$)	Natural log	Log_{10}	Log_2	Log_{10}	Log_{10}
Central beta (β) estimate	0.35	0.36	0.17	0.64	0.96
Lower beta (β) estimate (based on lower bound of 95% CI for HR)	0.16	0.05	0.07	0.32	0.54
Upper beta (β) estimate (based on upper bound of 95% CI for HR)	0.54	0.68	0.27	0.97	1.37

It is important to note that the concentration-response function from Aoki et al. (2016) uses hematocrit-adjusted blood Pb levels, rather than whole blood Pb levels as in Lanphear et al. (2018) and Ruiz-Hernandez et al. (2017). Whole blood Pb levels are commonly used as biomarkers in epidemiological studies and in physiologically-based pharmacokinetic (PBPK) modeling of blood Pb levels. Thus, we evaluated a potential correction factor for modeled whole blood Pb levels to derive hematocrit-adjusted blood Pb levels. Our methods for calculating hematocrit-adjusted blood Pb levels for use in the concentration-response function from Aoki et al. (2016) are described below in Section 4.3.3.

Equation 2, which estimates cases avoided, will hereafter be referred to as the health impact function. Exhibit 21 provides a comparison of beta estimates from each of our key studies by calculating the increased risk of CVD mortality per unit change in blood Pb (i.e. 1 µg/dL) based on the results from each study.

Exhibit 21. Increased Risk of CVD Mortality per Unit Change in Blood Pb, Based on Key Studies

Increased Risk of CVD Mortality per Unit Change in Blood Pb (Central Estimate and 95% CI)
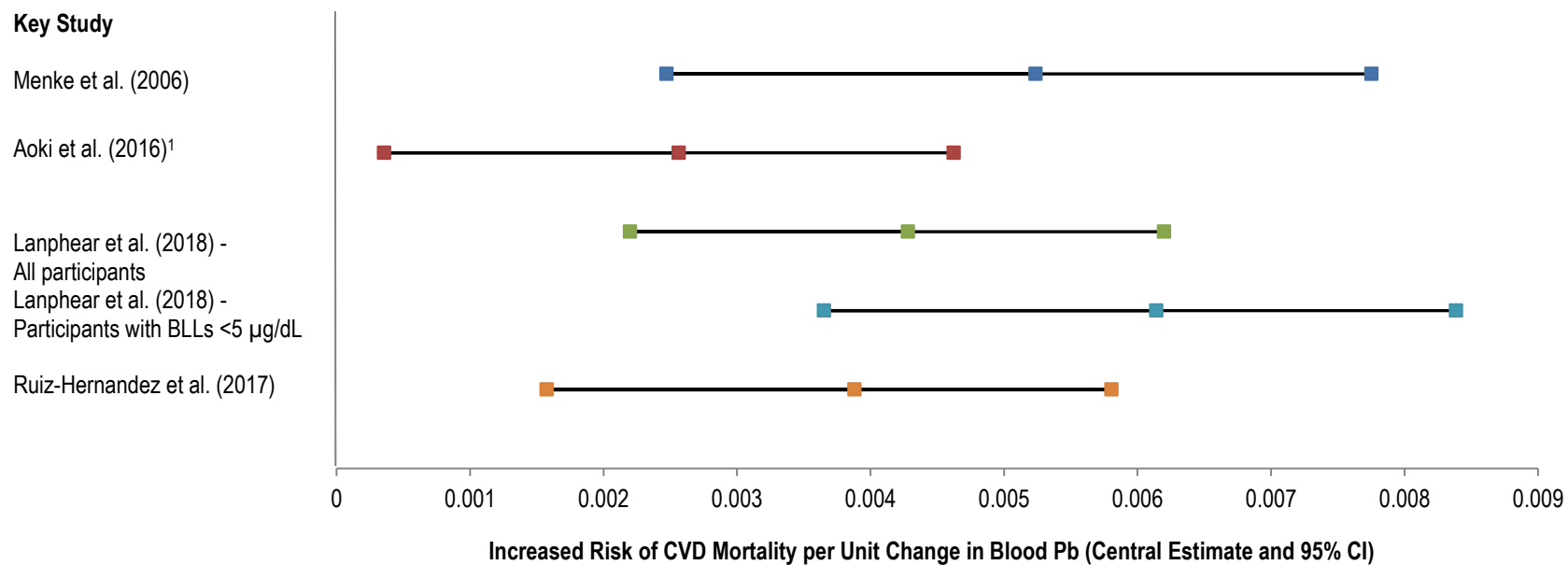
[1] Blood Pb corrected for hematocrit levels.

4.3 Example Application of the Health Impact Functions

To demonstrate use of the health impact functions based on our three selected key studies, we will estimate the impact on CVD mortality of a hypothetical regulation that would result in a 0.1 µg/dL decrease in blood Pb levels for 1 million people between the ages of 40 and 80 years old. In Sections 4.3.1 and 4.3.2, we discuss the baseline hazard rates of CVD mortality and the population numbers, respectively, that we will use in these hypothetical examples. Section 4.3.3 describes the potential hematocrit correction for modeled blood Pb levels that was explored for use with the Aoki et al. (2016) concentration-response function. Our estimated changes in CVD mortality based on results from our three selected key studies are displayed in Section 4.3.4.

4.3.1 Baseline Hazard Rate of CVD Mortality

For the baseline hazard rate of CVD mortality (i.e., input of y_1 in the health impact function), we used age- and sex-specific CVD mortality rates[12] from the CDC's Wide-Ranging Online Data for Epidemiologic Research (WONDER) database. For the age-specific rates, 10-year age categories were used (e.g., rate for 40-49 year olds). We obtained data for the most recent year available in WONDER, which was 2014. Exhibit 22 displays the CVD mortality rates used in our hypothetical example.

Exhibit 22. Age- and Sex-Specific Cardiovascular Disease Mortality Rates in the United States in 2014, Based on CDC's WONDER Database

Age (years)	Sex	Number of Deaths	Total Population	CVD Mortality Rate, Y_1
40-49	M	16,164	20,566,856	7.86E-04
	F	7,886	20,912,669	3.77E-04
50-59	M	47,045	21,521,569	2.19E-03
	F	21,930	22,560,689	9.72E-04
60-69	M	74,155	16,127,000	4.60E-03
	F	39,275	17,764,398	2.21E-03
70-80	M	98,852	9,151,537	1.08E-02
	F	74,989	11,107,883	6.75E-03
Total (40-80 years)	**M**	**236,216**	**67,366,962**	**3.51E-03**
	F	**144,080**	**72,345,639**	**1.99E-03**
	Both	**380,296**	**139,712,601**	**2.72E-03**

Source: CDC - National Center for Health Statistics (2014)

4.3.2 Population

In our example scenario we are assuming benefits will be experienced by 1 million people, which is approximately 0.7% of the U.S. population aged 40-80 years old. Thus, we assumed that 0.7% of

---

[12] ICD Codes:I00-I99

individuals in each age and sex category would experience an exposure reduction. The total population in each category affected by our hypothetical example is presented in Exhibit 23.

Exhibit 23. Population Experiencing Exposure Reductions in our Hypothetical Example, By Age and Sex Categories

Age (Years)	Gender	Total Population	Population Experiencing Exposure Reductions (0.7% of Total Population)
40-49	M	20,566,856	147,208
40-49	F	20,912,669	149,683
50-59	M	21,521,569	154,042
50-59	F	22,560,689	161,479
60-69	M	16,127,000	115,430
60-69	F	17,764,398	127,150
70-80	M	9,151,537	65,503
70-80	F	11,107,883	79,505
Total (40-80 years)	**M**	67,366,962	482,182
Total (40-80 years)	**F**	72,345,639	517,818
Total (40-80 years)	**Both**	139,712,601	1,000,000

4.3.3   Hematocrit Correction for the Aoki et al. (2016) Concentration-Response Function

As previously stated, the concentration-response function from Aoki et al. (2016) relies on hematocrit-adjusted blood Pb levels, as opposed to whole blood Pb levels. Whole blood Pb levels are the metric often used in epidemiologic studies and output from models, including EPA's Adult Lead Methodology and the *beta* version of the All Ages Lead Model. Therefore, to explore the difference of using whole blood Pb output when we implement the function from Aoki et al. (2016), we developed an approach to estimate modeled hematocrit-adjusted blood Pb levels by applying a hematocrit correction factor to whole blood Pb levels.

When developing this correction factor, we noted that hematocrit levels depend on numerous factors, including but not limited to sex, age, and whole blood Pb levels at the time of testing. Therefore, the correction factors we developed are based on the geometric mean hematocrit level for a given sex, age, and blood Pb quartile. Since we are calculating benefits estimates for CVD mortality for each sex and each 10-year age group (i.e. 40-49 year olds, 50-59 year olds, etc.), we apply a hematocrit correction to our resulting whole blood Pb estimates for each sex and age group within the relevant range of blood Pb. Our hematocrit correction equation is summarized as follows:[13]

---

[13] This hematocrit correction equation follows the basic form of the hematocrit correction introduced by deSilva (1984) and used in Aoki (2016).

$$B_C = B * \frac{H}{Ht_{GM}}$$
(Equation 4)

Where:

B_C =   Hematocrit-corrected blood Pb

B =   Whole blood Pb

H =   Geometric mean hematocrit level for the population (i.e., individuals between 40 and 80 years old)

Ht_{GM} = Geometric mean hematocrit level for the particular sex/age group, for the relevant range of whole blood Pb level

Using data from NHANES 2013-2014, we calculated hematocrit correction factors, $\frac{H}{Ht_{GM}}$, to apply to whole blood Pb levels. These correction factors are presented in Exhibit 24 below. As shown in the above equation, the values are simply multiplied by the whole blood Pb levels to obtain an estimate of hematocrit-corrected blood Pb levels.

Exhibit 24.   Proposed Hematocrit Correction Factors by Sex, Age and Quartile of Blood Pb

Sex and Age (Years)	Blood Pb Quartile			
	1st (0 to < 0.76 µg/dL)	2nd (0.76 to <1.12 µg/dL)	3rd (1.12 to <1.71µg/dL)	4th >1.71 µg/dL
Male				
40-49	0.92	0.93	0.93	0.94
50-59	0.97	0.96	0.96	0.94
60-69	0.99	0.94	0.95	0.95
70-80	1.03	0.98	0.99	0.98
Female				
40-49	1.07	1.04	1.05	1.05
50-59	1.05	1.04	1.02	1.01
60-69	1.05	1.02	1.03	1.04
70-80	1.04	1.05	1.05	1.04

Whole blood Pb levels are taken from NHANES 2013-2014 for the same age and sex categories (column 1 of Exhibit 25) for which CVD mortality rates were evaluated. For this hypothetical example we then subtracted 0.1 µg/dL from the whole blood Pb levels to determine the "post-rule" whole blood Pb levels (column 2 of Exhibit 25). To utilize these whole blood Pb levels in the benefits functions derived from Aoki et al. (2016) we then multiplied the pre and post rule blood Pb levels by

the appropriate hematocrit correction factor from Exhibit 16 to come up with hematocrit corrected baseline and post-rule blood Pb levels (columns 3 and 4 of Exhibit 25, respectively).

Exhibit 25. **Geometric Mean Whole Blood Pb Levels from NHANES 2013-2014, With and Without Hematocrit Correction**

Age (Years)	Sex	Whole Blood Pb (µg/dL)		Hematocrit-Corrected Blood Pb (µg/dL)	
		Pre-rule (Column 1)	Post-rule (Column 2)	Pre-rule (Column 3, x_1)	Post-rule (Column 4, x_2)
40-49	M	1.11	1.01	1.03	0.94
	F	0.77	0.67	0.80	0.72
50-59	M	1.33	1.23	1.28	1.18
	F	1.04	0.94	1.08	0.98
60-69	M	1.40	1.30	1.33	1.24
	F	1.24	1.14	1.28	1.18
70-80	M	1.72	1.62	1.68	1.61
	F	1.32	1.22	1.39	1.28

4.3.4 Results

Using the inputs as described in the preceding sections we calculated hypothetical benefits for a 0.1 µg/dL decrease in blood Pb levels for 1 million people (0.7% of the population). The results of this analysis using the concentration-response functions from our selected key studies are presented in Exhibit 26 and Exhibit 27.

Exhibit 26.   Estimates of Avoided CVD Mortality Cases Using our Hypothetical Example and Selected Concentration-Response Functions

Age Group (Years)	Gender	Avoided Cases of CVD Mortality Per Year (95% CI)[a]				
		Menke et al. (2006)	Aoki et al. (2016)	Ruiz-Hernandez et al. (2017)	Lanphear et al. (2018) – All Participants	Lanphear et al. (2018) – BLLs <5 µg/dL Only
40-49	M	3.7 (1.7, 5.6)	1.7 (0.2, 3.1)	2.6 (1.0, 4.1)	2.9 (1.5, 4.4)	4.3 (2.5, 6.2)
	F	2.6 (1.2, 4.0)	1.0 (0.1, 1.8)	1.9 (0.7, 2.9)	2.1 (1.0, 3.1)	3.1 (1.8, 4.4)
50-59	M	8.8 (4.0, 13.6)	4.1 (0.5, 7.5)	6.4 (2.5, 9.9)	7.1 (3.5, 10.6)	10.5 (6.0, 14.9)
	F	5.3 (2.4, 8.2)	2.4 (0.3, 4.5)	3.8 (1.5, 5.9)	4.3 (2.1, 6.4)	6.3 (3.6, 8.9)
60-69	M	13.2 (6.0, 20.4)	6.1 (0.8, 11.3)	9.6 (3.7, 14.8)	10.6 (5.3, 15.9)	15.7 (9.0, 22.3)
	F	7.9 (3.6, 12.2)	3.6 (0.5, 6.8)	5.7 (2.2, 8.9)	6.4 (3.2, 9.5)	9.4 (5.4, 13.4)
70-80	M	14.3 (6.4, 22.1)	4.4 (0.6, 8.3)	10.3 (4.0, 16.0)	11.5 (5.7, 17.2)	17.0 (9.7, 24.2)
	F	14.2 (6.4, 21.9)	6.5 (0.9, 12.1)	10.3 (4.0, 15.9)	11.4 (5.7, 17.1)	16.9 (9.6, 24.0)
Total (40-80)	**M**	39.9 (18.0, 61.8)	16.2 (2.2, 30.2)	28.9 (11.3, 44.7)	32.1 (16.0,48.1)	47.6 (27.1,67.6)
	F	30.0 (13.6, 46.3)	13.5 (1.8, 25.2)	21.8 (8.5, 33.6)	24.2 (12.0, 36.1)	35.7 (20.4, 50.7)
	Both	69.9 (31.6, 108.1)	29.7 (4.0, 55.4)	50.7 (19.8, 78.3)	56.3 (28.0, 84.1)	83.3 (47.5, 118.3)

[a] Assuming 0.1 µg/dL decrease in blood Pb levels in 0.7% of the U.S. population aged 40-80 years old.

Exhibit 27.   Estimates of Annual Monetary Benefits Using our Hypothetical Example and Selected Concentration-Response Functions

Age Group (Years)	Gender	Annual Monetary Benefits in Millions of Dollars (95% CI)[a,b]				
		Menke et al. (2006)	Aoki et al. (2016)	Ruiz-Hernandez et al. (2017)	Lanphear et al. (2018) – All Participants	Lanphear et al. (2018) – BLLs <5 µg/dL Only
40-49	M	36.4 (16.5, 56.2)	16.7 (2.3, 31.1)	26.4 (10.3, 40.7)	29.3 (14.6, 43.8)	43.3 (24.8, 61.5)
	F	26.0 (11.8, 39.9)	9.5 (1.3, 17.7)	18.9 (7.4, 29.0)	20.9 (10.5, 31.2)	30.9 (17.7, 43.6)
50-59	M	87.9 (39.7, 136.0)	40.4 (5.4, 75.2)	63.8 (24.9, 98.4)	70.8 (35.2, 105.8)	104.7 (59.8, 148.8)
	F	52.8 (23.9, 81.5)	24.3 (3.3, 45.2)	38.3 (15.0, 59.1)	42.5 (21.2, 63.5)	62.9 (35.9, 89.1)
60-69	M	131.5 (59.4, 203.5)	60.4 (8.1, 112.5)	95.3 (37.3, 147.2)	105.9 (52.6, 158.3)	156.7 (89.4, 222.7)
	F	78.9 (35.7, 122.0)	36.2 (4.9, 67.5)	57.2 (22.4, 88.3)	63.5 (31.6, 94.9)	93.9 (53.6, 133.4)
70-80	M	142.1 (64.0, 220.1)	44.1 (5.9, 82.4)	102.9 (40.2, 159.1)	114.3 (56.7, 171.0)	169.3 (96.4, 240.9)
	F	141.3 (63.8, 218.5)	64.9 (8.7, 120.8)	102.4 (40.1, 158.1)	113.7 (56.5, 170.0)	168.2 (96.0, 239.0)
Total (40-80)	**M**	397.9 (179.6, 615.8)	161.6 (21.7, 301.2)	288.4 (112.8, 445.4)	320.2 (159.1, 478.9)	474.0 (270.3, 673.9)
	F	299.0 (135.2, 461.9)	134.9 (18.2, 251.2)	216.8 (84.9, 334.5)	240.7 (119.8, 359.5)	355.9 (203.3, 505.2)
	Both	696.9 (314.7, 1077.7)	296.4 (39.9, 552.4)	505.2 (197.7, 779.9)	561.0 (278.9, 838.4)	829.9 (473.6, 1179.1)

[a] Assuming 0.1 µg/dL decrease in blood Pb levels in 0.7% of the U.S. population aged 40-80 years old.
[b] Calculated using a VSL equal to $9.97 million in 2014$ (U.S. EPA, 2017).

As shown in Exhibit 26 and Exhibit 27, the estimates from Aoki et al. (2016) are the lowest of all the key studies identified. The results using all participants from Lanphear et al. (2018) and Ruiz-Hernandez et al. (2017) are very similar. The function from Lanphear et al. (2018) based on analysis of participants with blood Pb levels below 5 μg/dL only results in the highest estimates of avoided CVD mortality cases. As can be seen in Exhibit 25, the hematocrit correction made very little difference to the estimated blood Pb levels and thus to the associated benefits, particularly when looking at national level averages rather than specific individuals. Additionally, there was fluctuation in the correction factor in different age groups (sometimes less than one, sometimes greater, see Exhibit 24). Therefore, it is not necessary to use the correction when using modeled whole blood lead levels with a function derived from the Aoki hematocrit corrected analysis.

5. Generalizability of the Concentration-Response Functions

In order for concentration-response functions to be useful for a benefits analysis, the functions should be generalizable to a large portion of the population. To properly use the concentration-response functions derived in the previous section, they must be applied to the appropriate population (Section 5.1), the appropriate blood Pb concentrations (Section 5.2), and over the appropriate time for the appropriate blood Pb metric (Section 5.3).

5.1   Generalizability to the Adult Population

Aoki et al. (2016) and Lanphear et al. (2018) derived effect estimates only for the general population. The authors did not evaluate whether this function would vary by age or for different sectors of the population. There is some uncertainty in regards to the impact of blood Pb on certain populations given the age-cohort effect, where age is correlated with both increased likelihood of disease (irrespective of Pb exposure) and increased blood Pb. Additionally, there are certain disease states that likely affect retention and elimination of Pb (irrespective of causal relationships). For example, as pointed out in the previous peer review, glomerular filtration rate decreases naturally with age, coincident with blood in Pb increasing with age due to the cohort effect (U.S. EPA, 2015).

As shown in Exhibit 13, Ruiz-Hernandez et al. (2017) investigated interactions in the association between blood Pb and CVD mortality by sex, smoking status and survey period. Interactions for sex and smoking status failed to reach significance (p = 0.07), and no interaction was found for survey period (p = 0.47). Menke et al. (2006) also evaluated associations in different portions of the population, as displayed in Exhibit 12, and did not find any significant interactions for any groups.

Based on the above findings from Ruiz-Hernandez et al. (2017) and Menke et al. (2006), and the fact that the concentration-response functions from our key studies are based on sampling of the U.S. adult population from NHANES, we conclude that each function can be applied to the general population of U.S. adults. However, it should be noted that there may be some subsets of the population for which there are interactions or a different form of the association between the blood Pb levels and CVD mortality that have yet to be evaluated.

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

In an assessment of a previous version of this report, members of the peer-review panel stated that it is appropriate to use data from NHANES III despite the trend to lower overall Pb exposures, based on toxicokinetic and toxicological mechanistic evidence relating Pb to adverse cardiovascular outcomes (U.S. EPA 2015). The reviewers pointed out that there is no identified level of exposure below which the effects of Pb do not occur. Further, EPA risk assessment guidelines allow for the extrapolation of concentration-response relationships from higher doses in the absence of directly relevant data in the low dose region. In addition, one reviewer noted that, although blood Pb levels have decreased over time, there are still older individuals in the U.S. who have high Pb body burden.

These endogenous Pb exposures can result in higher blood Pb levels than the estimated average blood Pb level in the U.S.

While the blood Pb levels examined in each of our key studies are higher than the current average blood Pb levels in the U.S., the studies published since the last peer review include a newer cohort of NHANES which has lower mean blood Pb levels. Mean blood Pb levels in the key studies ranged from 1.73 μg/dL to 2.71 μg/dL. These levels are higher than the average blood Pb level for adults aged 40-80 in NHANES 2013-2016, which is approximately 1.2 μg/dL. Lanphear et al. (2018) looked at the difference in the rate of increase in relative risk in the two phases of the NHANES III cohort. They found the relationship was steeper for participants who were studied during NHANES-III phase 2 (1991–94) than phase 1 (1988–91). Ruiz-Hernandez et al. (2017) found that the association of blood Pb with CVD mortality endpoints was similar across survey periods (NHANES III (1988–94) and NHANES 1999–2004). Collectively, these studies support the hypothesis that there is not an identified threshold for Pb in the outcome of CVD mortality, and the association between blood Pb and CVD mortality is expected to hold in cohorts with declining blood Pb levels.

Another consideration in determining the blood Pb range over which the concentration-response functions should be applied is the level of detection (LOD) of blood Pb in NHANES. As shown in Exhibit 28, the LOD in the NHANES surveys used by Aoki et al. (2016) ranged from 0.25 μg/dL to 0.3 μg/dL. Since the Menke et al. (2006) and Lanphear et al. (2018) study used NHANES III, the LOD was higher: 1.0 μg/dL. LODs for the NHANES data used by Ruiz-Hernandez et al. (2017) ranged from 0.25 μg/dL to 1.0 μg/dL.

Exhibit 28. Level of Detection for Whole Blood Pb Levels in 1999-2010 NHANES

NHANES Dataset	Blood Pb LOD (μg/dL)	Value for Measurements Below LOD
2009-2010	0.25	LOD/SQRT(2)
2007-2008	0.25	LOD/SQRT(2)
2005-2006	0.25	LOD/SQRT(2)
2003-2004	0.25	LOD/SQRT(2)
2001-2002	0.3	LOD/SQRT(2)
1999-2000	0.3	LOD/SQRT(2)
Source: Personal communication with NHANES		

In our example application of the health impact function, all gender- and age- specific mean blood Pb levels from NHANES (as shown in Exhibit 25) are greater than the LODs used in the Aoki et al. (2016) study, but some levels are lower than the LODs used in Menke et al. (2006), Lanphear et al. (2018) and Ruiz-Hernandez et al. (2017). Therefore, we are applying the concentration-response functions from these latter three studies to blood Pb levels that were not able to be quantified in the analyses. However, given that no threshold for the adverse health effects of Pb has been identified, it may be argued that it is appropriate to apply a concentration-response function to blood Pb levels below the LOD used in the study from which it was derived. Additionally, despite the

trend of decreasing mean exposures to Pb, all studies examined blood Pb levels that are equivalent to those found in individuals today.

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

Questions still remain about the time frame over which Pb biomarkers most accurately represent 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, 2013b, p. lxxxv). These uncertainties are partially addressed by the key studies identified since the ISA was published. They cannot be fully addressed due to the fact that all of the studies are based on a biomarker measurement taken at a single point in time per study subject. Therefore, there is not a clear answer to issues regarding cessation lag and latency,[14] and there is uncertainty in which conceptual model best represents the relationship between the biomarkers of Pb exposure and current risk of CVD mortality.

Previous reviewers of a similar approach noted there are strengths and drawbacks to using either bone or blood Pb as the biomarker of exposure (U.S. EPA, 2015). For example, the blood Pb biomarker is the most frequently used, and it is useful for measuring shorter term changes in exposure (e.g., a renovation causing exposure). Additionally, due to its greater bioavailability, Pb in blood will have the ability to impact cardiovascular health whereas Pb in bone will first need to be remobilized out of the bone. On the other hand, given the longer half-life of Pb in bone, reviewers noted that bone Pb may be a better marker of exposure for diseases that are impacted by longer term Pb exposures. However, there are few available studies that use bone Pb data. In addition, it is difficult to verify the exposure associated with bone Pb without a diary or basis for reconstructing historic data (U.S. EPA, 2015).

Given these uncertainties, it is unclear what model best relates the available biomarkers to CVD mortality risk. The main conceptual models which could explain the relationship between CVD mortality risk and biomarkers of Pb exposure are presented below. Other conceptual models that incorporate multiple peaks or different biomarkers are also possible.[15]

There are similar conceptual models to those outlined below for blood Pb when considering bone Pb. However, at this time we do not recommend using bone Pb to predict CVD mortality in benefits analysis. This is because of the uncertainties in modeling bone Pb levels with available PBPK models, and that the fact that currently only Weisskopf et al. (2009, 2015) has evaluated the relationship between bone Pb and CVD mortality risk. Therefore, we have opted not to present the potential bone Pb conceptual models in this report.

---

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

[15] Note that Models 1 and 2 can be considered special cases of Model 3 in which latency is set equal to zero.

Conceptual Model 1. Current CVD mortality risk = f(one-time blood Pb)

Using a health impact function based on any of our identified key studies, or any other study located in our literature review, assumes that conceptual model 1 is true, or is an appropriate approximation of the true underlying exposure which is associated with CVD mortality risk. This is because all of the studies presented in this report used a one-time measurement of blood Pb level to model the potential relationship between blood Pb and CVD mortality. Since there are currently no studies or data sources such as NHANES that allow for the evaluation of the risk of CVD mortality based on multiple blood Pb measurements in the same individual, conceptual model 1 is the only model for which requisite data are available at this time. This results in uncertainty because blood Pb is reflective of both recent exposures (<30 days) from exogenous sources and past exposures (years to decades) from endogenous releases of Pb that was previously stored in tissues (e.g., bone) (National Toxicology Program, 2012; U.S. EPA, 2013b).

To apply this model in benefits analysis, we would use baseline and with-rule predicted blood Pb levels estimated for a population of a specified age and a given exposure scenario and apply that single blood Pb level change to the health impact functions presented in this paper to determine the number of cases of CVD mortality avoided. In order to account for the data gap in latency in our hypothetical calculations, we make the assumption that the distribution for the age of the individuals dying from cardiovascular related causes due to Pb exposure is the same as the distribution of cardiovascular mortality by age and sex irrespective of the cause. EPA used an analogous approach for cancer incidence in the Proposed Formaldehyde Standards for Composite Wood Products Implementation Rule Economic Analysis (U.S. EPA, 2013a).

Conceptual Model 2. Current CVD mortality risk = f(average blood Pb over x years)

If this model represents the true relationship between blood Pb and CVD mortality, it is unclear whether the health impact function presented in this report would over- or underestimate the number of CVD mortality cases. The single blood Pb measurement that forms the basis of the analyses in our key studies 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. Average blood Pb levels in adults may correlate with one time measures such as those in NHANES, assuming exposure is relatively steady over the individual's lifetime.

If it was deemed appropriate to utilize this conceptual model for benefits analysis, a decision would need to be made regarding the appropriate number of years over which to average blood Pb levels. We would then conduct blood Pb modeling for both baseline and with-rule scenarios for each year of life and average over the specified time frame. Lastly, we would utilize the health impact function to determine how the change in average blood Pb level over the specific time frame would result in a change in the number of cases of CVD mortality. Averaging the modeled blood Pb over a specified period of time would then be thought to approximate the one time measure taken in the studies. Peer reviewers noted the high correlation with blood and bone Pb, and the correlation with lifetime

exposure due to Pb being mobilized from the bone (U.S. EPA, 2015). In this case, the one-time blood Pb measurement of NHANES is assumed in most participants to represent steady state and therefore to be a proxy of lifetime average exposure.

Conceptual Model 3. Current CVD mortality risk = f(average blood Pb over x years) + latency

As with model number two, it is unclear if the selected health impact function would over- or underestimate the number of CVD mortality cases if this conceptual model is assumed to be true. This is because it is uncertain whether the blood Pb levels used in the analyses presented in this report relate to recent exogenous exposures or to past exposures re-released endogenously.

To conduct benefits analyses using this conceptual model, we would have to select the number of years over which it would be appropriate to average blood Pb levels. In addition, a decision would need to be made regarding the timeframe for the latency period. That is, an assumption would need to be made regarding the number of years between the Pb exposures and the avoided CVD mortality effect. Then, as for conceptual model 2, baseline and with-rule blood Pb levels would be modeled and averaged over the appropriate time frame. The health impact function would be used to estimate changes in CVD mortality, the monetization of which would depend on the latency period selected.

Although, as previously stated, it is unclear whether the health impact function would over- or underestimate benefits, using a conceptual model that incorporates latency would result in a lower benefits estimate compared to a conceptual model which does not incorporate latency. This is because although the same number of cases would be prevented as with Conceptual Model 2, benefits would be realized later than predicted when not considering latency. Since benefits in the future are discounted, not including this assumption would result in an overestimation of monetized benefits if there is indeed a latency period for the effects of Pb on CVD mortality. As part of the benefits estimation, an assumption about latency could be built in to provide a sensitivity analysis for results.

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

Under conceptual model 4, peak exposures are assumed to be the most important in predicting risk. If this model is assumed to be true, it would be hard to predict the direction in which our analyses would be biased. This is because we do not know when the NHANES Pb measurements were taken in relation to the timing of the peak Pb exposure. However, it is unlikely that on average, the participants in NHANES are sampled during peak exposures. External exposures are represented in blood Pb with a half-life of approximately 30 days, during which Pb is eliminated or stored in bone. 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.

To use this conceptual model in benefits analysis, blood Pb modeling would need to be conducted over the adult life of an individual for baseline and with-rule scenarios. Assumptions would need to be made regarding timeframe, including how many years to model and how the peak level should be defined (e.g., daily blood Pb level, average annual blood Pb level). Once these decisions are

made, the highest value from the modeled output for baseline and with-rule scenarios would be input into the health impact functions to determine how the number of CVD mortality cases changes with a given rule.

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

The hypothetical examples presented in Section 4.3 used point estimates for each of the parameters (y_0, β, and *pop*). However, in reality each of the parameters used in the functions are uncertain and variable. Consequently, as with any benefits analysis, there is uncertainty and variability of the concentration-response functions and the health impact functions. 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 functions (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 and Variability in the Concentration-Response Functions

Recall from Section 4.2 the concentration-response functions from each study are of the form:

$$\Delta CVD\ Mortality = \ y_1 \left(1 - e^{\beta \log_z \left(\frac{x_2}{x_1} \right)} \right)$$

where y_1 is the probability of the adverse health effect (e.g., CVD mortality), x_1 and x_2 are the pre- and post-rule blood Pb level, respectively, $\log_z$ indicates the type of log transformation used in the statistical analyses, and β is specific to each study. The uncertainty and variability associated with each of these parameters is discussed in the following sections.

6.1.1 Effect (β) Estimate

The beta estimates in each study have inherent uncertainties associated with them. For example, sampling uncertainty is the uncertainty associated with sampling a random sample of a group as opposed to every individual in the group, and is present in any study using NHANES data to represent the larger general population. This uncertainty can be characterized by using a distribution of estimates for the beta as opposed to the single value that represents the central beta estimate. An example of the lower and upper bound estimates of the number of avoided CVD deaths was calculated in our hypothetical example in Section 4.3 using the upper and lower bounds of the 95% confidence interval on the central beta estimates.

As for variability associated with the β estimate, Aoki et al. (2006) and Lanphear et al. (2018) did not examine effect modification. However, this was assessed in Menke et al. (2016) and Ruiz-Hernandez et al. (2017); no statistically significant interactions were found in either study.

There is also an uncertainty in regard to the NHANES 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 each key study is that findings 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, 2013b). Therefore, it is unclear whether the impact of Pb on CVD mortality risk observed in each key study is associated with current, past, or cumulative exposures.

It is possible that the relationship predicted by using a single blood Pb measure 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 Marc Weisskopf, 2013; Rothman, 1998).

6.1.2   Blood Pb Estimates

To use the concentration-response and subsequent health impact function derived from the Aoki et al. (2016) paper, we needed to develop a method by which to correct for hematocrit levels. This is because Aoki et al. (2016) utilized hematocrit-corrected blood Pb levels in the model we selected. The other three key studies do not require this correction. Reviewing Exhibit 24, it can be seen that these hematocrit correction factors modify the whole blood Pb measurements by very small amounts. However, in Aoki et al. (2016) the model without the hematocrit correction did not find a statistically significant result. To compare how the results may vary if we did not implement the correction but instead simply used whole blood Pb levels, we re-ran our hypothetical example using our selected function (model A1) from Aoki et al. (2016) and whole blood Pb levels from NHANES 2013-2014, as shown in Exhibit 29.

Exhibit 29. Comparison of Results Using Hematocrit Corrected versus Whole Blood Pb

Age Group (Years)	Gender	Results Using Hematocrit Corrected Blood Pb Levels		Result Using Whole Blood Pb	
		Annual Cases Avoided	Annual Benefits (Millions)[a]	Annual Cases Avoided	Annual Benefits (Millions)[a]
40-49	M	1.7 (0.2,3.2)	16.7 (2.3,31.1)	1.7 (0.2,3.2)	16.7 (2.3,31.1)
	F	**1.0 (0.1,1.8)**	**9.5 (1.3,17.7)**	**1.2 (0.2,2.3)**	**12.0 (1.6,22.2)**
50-59	M	4.1 (0.6,7.7)	40.4 (5.4,75.2)	4.1 (0.6,7.7)	40.4 (5.4,75.2)
	F	2.5 (0.3,4.6)	24.3 (3.3,45.2)	2.5 (0.3,4.6)	24.3 (3.3,45.2)
60-69	M	6.1 (0.9,11.5)	60.4 (8.1,112.5)	6.1 (0.9,11.5)	60.4 (8.1,112.5)
	F	3.7 (0.5,6.9)	36.2 (4.9,67.5)	3.7 (0.5,6.9)	36.2 (4.9,67.5)
70-80	**M**	**4.5 (0.6,8.4)**	**44.1 (5.9,82.4)**	**6.6 (0.9,12.4)**	**65.1 (8.7,121.5)**
	F	6.6 (0.9,12.3)	64.9 (8.7,120.8)	6.6 (0.9,12.3)	64.9 (8.7,120.8)
Total (40-80 years)	**M**	**16.4 (2.3,30.8)**	**161.6 (21.7,301.2)**	**18.5 (2.6,34.8)**	**182.6 (24.5,340.3)**
	F	**13.7 (1.9,25.7)**	**134.9 (18.2,251.2)**	**13.9 (1.9,26.1)**	**137.4 (18.5,255.8)**
	Both	**30.0 (4.2,56.4)**	**296.4 (39.9,552.4)**	**32.4 (4.5,60.9)**	**320.0 (43.0,596.1)**

[a] Calculated using a VSL equal to $9.97 million in 2014$ (U.S. EPA, 2017).
Note: Results that differed when using whole blood Pb versus hematocrit corrected blood Pb are highlighted in bold.

These results demonstrate that performing the analysis without the hematocrit correction only changed the results for two populations: females aged 40-49 years old and males aged 70-80 years old. The reason these two populations varied is because a different hematocrit correction factor was applied in the pre- versus post-rule scenario. In all other instances, the pre- and post-rule mean blood Pb levels fell into the same quartile and thus had the same hematocrit correction factor (see Exhibit 24). Consequently the ratio between pre- and post- blood Pb levels, which determines the risk of CVD mortality based on the Aoki et al. (2016) function, was the same with and without the hematocrit correction; therefore, the benefits estimates remained the same. This finding raises the question of whether the hematocrit correction used in our analysis is necessary. For a rule that decreases mean blood Pb levels by only a minimal amount (for example, by 0.1 µg/dL as in our hypothetical scenario), the correction may not be necessary since mean blood Pb levels will likely remain in the same quartile. However, for a rule that may result in a greater change in blood Pb

levels, applying the hematocrit correction may result in a more substantial impact as blood Pb levels are more likely to shift between quartiles in the pre- and post- rule scenarios. It is also worth noting that applying a hematocrit correction based on more finely grouped blood Pb quantiles may result in larger differences between hematocrit-corrected blood Pb and whole blood Pb results. Using a smaller quantile than the quartiles used in this analysis, such as a decile, would make it more likely that smaller changes in mean blood Pb would cause a quantile shift, and thus would create differences in the hematocrit-correction factor between pre- and post- rule scenarios.

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, Aoki et al. (2016) assumed that the linear function between log of blood Pb and log of CVD mortality risk best represented the concentration-response relationship. A spline analysis was conducted and did not indicate any non-linearity. Lanphear et al. (2018) assessed concentrations of Pb in blood both as a continuous variable and categorically with tertiles. They also fitted five-knot restricted cubic splines to visualize the shape of the dose-response relation of concentrations of Pb in blood for all-cause mortality, CVD mortality, and ischemic heart disease mortality, and to investigate whether the relations should be judged linear or log-linear. Lanphear et al. (2018) concluded that the restricted cubic splines models indicated that adjusted HRs were steeper at lower concentrations of Pb in blood than at higher concentrations. 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. This was not explored by Aoki et al. (2016).

6.2   Uncertainty and Variability in the Health Impact Function

Health impact functions were derived from the concentration-response functions. Health impact functions allow for a quantification of the number of cases avoided among affected populations, as illustrated in our hypothetical examples. As a reminder, the form of the health impact function is:

$$Cases\ Avoided = \ y_1 \left(1 - e^{\beta \log_z \left(\frac{x_2}{x_1} \right)} \right) * pop \qquad \text{(Equation 2)}$$

Where:

y_1 = Baseline hazard rate of CVD mortality in baseline scenario (i.e., without the rule)

β = Beta coefficient, which represents the change in CVD mortality per unit change in blood Pb

$\log_z$ = Log transformation to the base z (e.g., $\log_{10}$)

x_2 = Blood Pb level associated with the rule

x_1 = Blood Pb level without the rule

pop = Population for whom the change in blood Pb occurs

In addition to the uncertainty associated with blood Pb measurements and the concentration-response function beta coefficient estimates (as discussed in the previous section), incorporating the baseline mortality rate and affected population into the equation adds additional uncertainty and variability to the benefits estimates. 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 must be characterized by the economists developing the analysis in the context of the rule. Sources of variability in the baseline mortality rates include 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 approximately 1 million people would be impacted, which is only 0.7% of the total U.S. adult population aged 40-80 years old. The number of people impacted will vary by the policy scenario being considered and will also vary according to many of the same sources of uncertainty and variability mentioned previously. 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. Conclusions

This report outlines a systematic approach to identify the most appropriate concentration-response function and associated health impact function to relate Pb exposure in adults to CVD mortality. Based on available data and *a priori* criteria, we selected four key studies – Aoki et al. (2016), Lanphear et al. (2018), Menke et al. (2006), and Ruiz-Hernandez et al. (2017) - from which to derive a function. We demonstrated the use of functions based on each study with a hypothetical example, which showed that the potential benefits of reduced Pb exposures in terms of avoided CVD mortality are significant and similar across studies. Given the weight of evidence associated with Pb exposure and CVD mortality, integrating this endpoint into future regulatory impact analysis will allow for a more comprehensive quantification and monetization of the adverse health effects potentially avoided with reduced Pb exposure.

When EPA published the Pb ISA in 2012, questions remained about the time frame over which Pb biomarkers most accurately represent risk. As stated in 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. lxxxv). In this report, we describe how the identified studies partially address the uncertainty over whether the observed associations between lead and CVD are applicable to current cohorts of individuals. However, they are unable to fully address the questions due to the fact they are all based on NHANES with one time blood lead measurements. No studies have examined repeated blood lead measures in the same individuals in order to explore their Pb exposure patterns over a lifetime. Since environmental levels of Pb have been decreasing as a result of interventions such as the Pb in gasoline ban, individuals examined in these studies may have had a higher exposure profile in childhood and early adulthood than those born in recent years. However, these higher exposures will likely be reflected in higher blood Pb levels in their NHANES blood Pb samples, as blood and bone Pb levels are correlated. Although their past blood Pb levels remain unknown, we know that, on average, older adults have higher blood Pb levels than younger adults sampled in NHANES.

Despite these uncertainties, we describe in the report several lines of evidence to suggest that it is appropriate to model the relationship between blood Pb and CVD mortality based on the available literature. Numerous studies examining different NHANES cohorts, including several published since the 2012 Pb ISA, have found significant associations between blood Pb and CVD mortality. Mean blood Pb levels in our four key studies ranged from 1.73 µg/dL to 2.71 µg/dL. While these levels are slightly higher than the average blood Pb level for adults aged 40-80 in NHANES 2013-2016, which is approximately 1.2 µg/dL, they are within a reasonable range of today's blood lead levels. In addition, the studies included individuals with blood Pb levels which overlap with the 2013-2016 NHANES mean levels. There is no identified level of exposure in the population below which the effects of Pb do not occur. Further, EPA risk assessment guidelines allow for the extrapolation of relationships observed at higher doses in the absence of directly relevant low dose observations.

The uncertainties regarding applicability of the observed associations to today's populations have also been partially addressed by evidence from several studies published since the 2012 Pb ISA. When comparing more recent NHANES data to older cohorts, these studies have found that associations between Pb and CVD mortality have either remained constant or increased in magnitude. For example, Ruiz-Hernandez et al. (2017) examined the associations between blood Pb and CVD mortality in two cohorts of NHANES: 1988-1994 and 1999-2004. The mean blood Pb levels in these cohorts were 3.2 and 1.9 μg/dL, respectively. The rate ratios for CVD mortality associated with a two-fold increase in blood Pb were 1.17 (1.04, 1.31) in NHANES 1988-1994 and 1.26 (1.05, 1.50) and in NHANES 1999-2004. When comparing results obtained for the two cohorts, the authors found no significant differences in the relationship between blood Pb and CVD mortality (p = 0.47). Lanphear et al. (2018) examined differences between the two phases of the NHANES III cohort. The authors found a steeper relationship (i.e., a greater increment of CVD mortality risk per increment of blood Pb) in participants who were studied during NHANES-III phase 2 (1991–94) than phase 1 (1988–91). Additionally, when Lanphear et al. (2018) investigated associations in all participants and in those with blood Pb <5 μg/dL only, the observed hazard ratios were higher in the subset of participants with the lowest blood Pb. Therefore, use of an observed concentration-response function based on older NHANES cohorts with higher blood Pb levels may in fact provide an underestimate of the association between Pb and CVD mortality, if the steeper slope is reflective of the true risk in today's population.

Collectively, the literature supports the hypothesis that there is not an identifiable population threshold for Pb and the outcome of CVD mortality, and that the association between blood Pb and CVD mortality is expected to hold in cohorts with declining blood Pb levels. Given the amount of available evidence, it is therefore now feasible to estimate both the health and monetary benefits of the reduced risk of CVD mortality due to lower blood Pb, as illustrated in this report.

8. References

American Heart Association. (2011). Cardiac Glossary. Retrieved from http://www.heart.org/HEARTORG/Conditions/HeartAttack/HeartAttackToolsResources/Cardiac-Glossary_UCM_303945_Article.jsp

Aoki, Y., Brody, D. J., Flegal, K. M., Fakhouri, T. H., Parker, J. D., & Axelrad, D. A. (2016). Blood Lead and Other Metal Biomarkers as Risk Factors for Cardiovascular Disease Mortality. *Medicine (Baltimore), 95*(1), e2223. doi:10.1097/md.0000000000002223

Atlas, S. (2007). The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm, 13*, 9-20.

Bertke, S. J., Lehman, E. J., Wurzelbacher, S. J., & Hein, M. J. (2016). Mortality of lead smelter workers: A follow-up study with exposure assessment. *American Journal of Industrial Medicine, 59*(11), 979-986.

Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S., & Kalayci, O. (2012). Oxidative Stress and Antioxidant Defense. *World Allergy Organization Journal, 5*(1), 9-19. doi:10.1097/wox.0b013e3182439613

Campese, V., Sindhu, R., Ye, S., Vaziri, N., & Jabbari, B. (2007). Regional expression of NO synthase, NAD(P)H oxidase and superoxide dismutase in the rat brain. *Brain Research, 1134*, 27-32.

Carsia, R., Forman, D., Hock, C., Nagele, R., & McIlroy, P. (1995). Lead alters growth and reduces angiotensin II receptor density of rat aortic smooth muscle cells. *Proc Soc Exp Biol Med, 210*, 180-190.

CDC - National Center for Health Statistics. (2014). *Underlying Cause of Death 1999-2014 on CDC WONDER Online Database, released 2015*. Retrieved from: http://wonder.cdc.gov/ucd-icd10.html

CDC. (1996). *Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994*. Atlanta, GA and Hyattsville, MD Retrieved from http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf

CDC. (2007). *Interpreting and Managing Blood Lead Levels < 10 µg/dL in Children and Reducing Childhood Exposures to Lead*. Morbidity and Mortality Weekly Report

Chai, S., & Webb, R. (1988). Effects of lead on vascular reactivity. *Environmental Health Perspectives, 78*, 85-89.

Chang, H., Chen, S., Tsao, D., Cheng, J., Ho, C., & Yu, H. (1997). Change of cardiac B-adrenoceptors in lead-exposed rats. *Toxicology, 123*, 27-32.

Chang, S. H., Cheng, B. H., Lee, S. L., Chuang, H. Y., Yang, C. Y., Sung, F. C., & Wu, T. N. (2006). Low blood lead concentration in association with infertility in women. *Environ Res, 101*(3), 380-386. doi:10.1016/j.envres.2005.10.004

Cocco, P., Fadda, D., Atzeri, S., Avataneo, G., Meloni, M., & Flore, C. (2007). Causes of death among lead smelters in relation to the glucose-6-phosphate dehydrogenase polymorphism. *Occupational and Environmental Medicine, 64*(6), 414-416. doi:10.1136/oem.2006.028779

Ding, Y., Vaziri, N., & Gonick, H. (1998). Lead-induced HTN. II. Response to sequential infusions of L-arginine, superoxide dismutase, and nitroprusside. *Environmental Research, 76*, 107-113.

Dursun, N., Arifoglu, C., Suer, C., & Keskinol, L. (2005). Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. *Biol Trace Elem Res, 104*, 141-150.

Farmand, F., Ehdale, A., Roberts, C., & Sindhu, R. (2005). Lead-induced dysregulation of superoxide dismutases, catalase, glutathione peroxidase, and guanylate cyclase. *Environmental Research, 98*, 33-39.

Gonick, H., Ding, Y., Bondy, S., N, i. Z., & Vaziri, N. (1997). Lead-induced HTN: interplay of nitric oxide and reactive oxygen species. *Hypertension, 30*.

Habermann, E., Crowell, K., & Janicki, P. (1983). Lead and other metals can substitute for Ca2+ in calmodulin. *Arch Toxicol, 54*, 61-70.

Holstege, C. P., Huff, J., Rowden, A., O'Malley, R., & Ramachandran, T. (2015). Pathophysiology and Etiology of Lead Toxicity. *MedScape News & Perspective*.

Kaji, T., Fujiwara, Y., Hoshino, M., Yamamoto, C., Sakamoto, M., & Kozuka, H. (1995). Inhibitory effect of lead on the proliferation of cultured vascular endothelial cells. *Toxicology, 95*, 87-92.

Kaji, T., Yamamoto, C., Sakamoto, M., & Kozuka, H. (1992). Inhibitory effect of lead on the release of tissue plasminogen activator from human vascular endothelial cells in culture. *Toxicology, 73*, 219-227.

Khalil-Manesh, F., Gonick, H., Weiler, E., Prins, B., Weber, M., Purdy, R., & Ren, Q. (1994). Effect of chelation treatment with dimercaptosuccinic acid (DMSA) on lead-related blood-pressure changes. *Environmental Research, 65*, 86-99.

Khalil, N., Wilson, J., Talbott, E., Morrow, L., Hochberg, M., Hillier, T., . . . Cauley, J. (2009). Association of blood lead concentrations with mortality in older women: a prospective cohort study. *Environmental Health, 8*(1), 1-10. doi:10.1186/1476-069x-8-15

Kishimoto, T., Oguri, T., Ueda, D., & Tada, M. (1995). Effect of lead on tube formation by cultured human vascular endothelial cells. *Arch Toxicol, 69*, 718-721.

Lahteenvuo, J., & Rosenzweig, A. (2012). Invited Review: The Role of Angiogenesis in Cardiovascular Aging. *Circ Res, 110*(9), 1252-1264.

Lanphear, B. P., Rauch, S., Auinger, P., & Allen, R. W. (2018). Low-level lead exposure and mortality in US adults: a population-based cohort study. *The Lancet Public Health, 3*(4), e177-e184.

Leggett, R. (1993). An age-specific kinetic model of lead metabolism in humans. *Environmental Health Perspectives, 101*(7), 598-616.

Lin, J. L., Lin-Tan, D. T., Hsu, C. W., Yen, T. H., Chen, K. H., Hsu, H. H., . . . Hsu, K. H. (2011). Association of blood lead levels with mortality in patients on maintenance hemodialysis. *The American Journal of Medicine, 124*(4), 350-358. doi:10.1016/j.amjmed.2010.10.022

Lustberg, M., & Silbergeld, E. (2002). Blood lead levels and mortality. *Archives of Internal Medicine, 162*(21), 2443-2449.

McElvenny, D., Miller, B., MacCalman, L., Sleeuwenhoek, A., van Tongeren, M., Shepherd, K., . . . Cherrie, J. (2015). Mortality of a cohort of workers in Great Britain with blood lead measurements. *Occupational and Environmental Medicine, 72*(9), 625-632.

MedlinePlus. (2014a). Medical Encyclopedia: Hematocrit. Retrieved from https://www.nlm.nih.gov/medlineplus/ency/article/003646.htm

MedlinePlus. (2014b). Medical Encyclopedia: Hemoglobin. Retrieved from https://www.nlm.nih.gov/medlineplus/ency/article/003645.htm

MedlinePlus. (2019). Hyperplasia. Retrieved from https://medlineplus.gov/ency/article/003441.htm

Menke, A., Muntner, P., Batuman, V., Silbergeld, E. K., & Guallar, E. (2006). Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults. *Circulation, 114*(13), 1388-1394. doi:10.1161/circulationaha.106.628321

Messner, B., & Bernhard, D. (2010). Cadmium and cardiovascular diseases: cell biology, pathophysiology, and epidemiological relevance. *Biometals, 23*(5), 811-822. doi:10.1007/s10534-010-9314-4

Møller, L., & Kristensen, T. S. (1992). Blood Lead as a Cardiovascular Risk Factor. *American Journal of Epidemiology, 136*(9), 1091-1100.

National Toxicology Program. (2012). *NTP Monograph on Health Effects of Low-Level Lead*.

Neuberger, J., Hu, S., Drake, K., & Jim, R. (2009). Potential health impacts of heavy-metal exposure at the Tar Creek Superfund site, Ottawa County, Oklahoma. *Environ Geochem Health, 31*(1), 47-59. doi:10.1007/s10653-008-9154-0

Personal Communication with Andy Menke (2013, 9/2/13).

Personal Communication with Marc Weisskopf (2013). [Phone Conversation on July 25th].

Prentice, R., & Kopp, S. (1985). Cardiotoxicity of lead at various perfusate calcium concentrations: functional and metabolic responses of the perfused rat heart. *Toxicology and Applied Pharmacology, 81*, 491-501.

Richardt, G., Federolf, G., & Habermann, E. (1986). Affinity of heavy metal ions to intracellular Ca2+ binding proteins. *Biochem Pharmacol, 35*, 1331-1335.

Rothman, K. (1998). *Modern Epidemiology*: Lippincott-Raven.

Ruiz-Hernandez, A., Navas-Acien, A., Pastor-Barriuso, R., Crainiceanu, C. M., Redon, J., Guallar, E., & Tellez-Plaza, M. (2017). Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988–2004. *International Journal of Epidemiology, 46*(6), 1903-1912.

Schober, S. E., Mirel, L. B., Graubard, B. I., Brody, D. J., & Flegal, K. M. (2006). Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study *Environmental Health Perspectives, 114*(10), 1538-1541.

Simons, T. (1993a). Lead-calcium interactions in cellular lead toxicity. *NeuroToxicology, 14*, 77-86.

Simons, T. (1993b). Lead transport and binding by human erythrocytes *in vitro*. *Pflugers Arch, 423*, 307-313.

Tellez-Plaza, M., Guallar, E., Howard, B. V., Umans, J. G., Francesconi, K. A., Goessler, W., . . . Navas-Acien, A. (2013). Cadmium exposure and incident cardiovascular disease. *Epidemiology, 24*(3), 421-429. doi:10.1097/EDE.0b013e31828b0631

Tsao, D., Yu, H., Cheng, J., Ho, C., & Chang, H. (2000). The change of B-adrenergic system in lead-induced HTN. *Toxicology and Applied Pharmacology, 164*, 127-133.

U.S. EPA. (1996). *Recommendations of the Technical Review Workgroup for Lead for an Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil*.

U.S. EPA. (2013a). *Economic Analysis of the Formaldehyde Standards for Composite Wood Products Act Implementing Regulations Proposed Rule*.

U.S. EPA. (2013b). *Integrated Science Assessment for Lead*. (EPA/600/R-10/075F). Research Triangle Park, NC

U.S. EPA. (2014). *Guidelines for Preparing Economic Analyses*.

U.S. EPA. (2015). *External Peer Review of EPA's Approach for Estimating Exposures and Incremental Health Effects from Lead due to Renovation, Repair, and Painting Activities in Public and Commercial Buildings.* Springfield, VA

U.S. EPA. (2017). *Economic Analysis of Proposed TSCA Section 6 Action on Trichloroethylene in Vapor Degreasing*. Washington, DC

Ueda, D., Kishimoto, T., Dekio, S., & Tada, M. (1997). Inhibitory effect of lead on tube formation by cultured human vascular endothelial cells. *Hum Cell, 10*, 283-291.

Valencia, I., Castillo, E., Chamorro, G., Bobadilla, R., & Castillo, C. (2001). Lead induces endothelium- and Ca2+ -independent contraction in rat aortic rings. *Pharmacol Toxicol, 89*, 177-182.

VanderWeele, T. J., Mumford, S. L., & Schisterman, E. F. (2012). Conditioning on intermediates in perinatal epidemiology. *Epidemiology, 23*(1), 1-9. doi:10.1097/EDE.0b013e31823aca5d

Vaziri, N., Ding, Y., Ni, Z., & Gonick, H. (1997). Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced HTN: effect of lazaroid therapy. *Kidney International, 52*, 1042-1046.

Vaziri, N., Lin, C., Farmand, F., & Sindhu, R. (2003). Superoxide dismutase, catalase, glutathione peroxidase and NADPH oxidase in lead-induced HTN. *Kidney International, 63*, 186-194.

Vaziri, N. D. (2008). Mechanisms of lead-induced hypertension and cardiovascular disease. *American Journal of Physiology: Heart and Circulatory Physiology, 295*(2), H454-H465. doi:10.1152/ajpheart.00158.2008

Wang, M., Xu, Y., Pan, S., Zhang, J., Zhong, A., Song, H., & Ling, W. (2011). Long-term heavy metal pollution and mortality in a Chinese population: an ecologic study. *Biol Trace Elem Res, 142*(3), 362-379.

Watts, S., Chai, S., & Webb, R. (1995). Lead acetate-induced contraction in rabbit mesenteric artery: interaction with calcium and protein kinase C. *Toxicology, 99*, 55-65.

Weisskopf, M. G., Jain, N., Nie, H., Sparrow, D., Vokonas, P., Schwartz, J., & Hu, H. (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. *Circulation, 120*(12), 1056-1064. doi:10.1161/circulationaha.108.827121

Weisskopf, M. G., Jain, N., Nie, H., Sparrow, D., Vokonas, P., Schwartz, J., & Hu, H. (2014). Erratum. *Circulation, 130*(5), e43. doi:10.1161/cir.0000000000000084

Weisskopf, M. G., Sparrow, D., Hu, H., & Power, M. C. (2015). Biased Exposure-Health Effect Estimates from Selection In Cohort Studies - Are Environmental Studies at Particular Risk? *Environmental Health Perspectives, 123*(11), 1113–1122.

Appendix A: Discussion of Møller and Kristensen (1992) and Weisskopf et al. (2009)

Møller and Kristensen (1992) examined the risk of developing coronary heart disease and cardiovascular disease using both fatal and nonfatal cases. The authors found a significant univariate association with total mortality, coronary heart disease, and cardiovascular disease. However, the association failed to reach significance when the models included potential confounders. It should be noted, though, that the association still remained positive (i.e., an increase in blood Pb was related to an increase in mortality) after adjustment for confounders. Møller and Kristensen (1992) did not examine the risk of CVD mortality without the non-fatal cases included in the analysis. A limitation of Møller and Kristensen (1992) is that no information is presented on the precision of blood Pb testing**.** This is relevant because the measurement of blood Pb levels at lower levels are sometimes imprecise, particularly for older lab tests aimed at detecting blood Pb levels above 10 µg/dL (CDC, 2007), resulting in an inability to detect subtle effects (U.S. EPA 2015). No data was provided in the Møller and Kristensen paper on the level of precision in their blood Pb analysis, but we know that the level of detection for blood Pb measurements has decreased in recent years and precision has increased. In comparison, the NHANES III data set used by two of the studies we evaluated (Menke et al., 2006; Schober et al., 2006) had a level of precision of less than 1 µg/dL for blood Pb levels lower than 20 µg/dL (CDC, 1996) and the level of detection has decreased for subsequent cohorts (See Exhibit 26). Weisskopf et al. (2009) did not state what the level of detection was in their study but they did explain that their blood Pb measurements had a coefficient of variation of 1 to 8 percent compared to CDC reference samples. Given the year of publication for the Møller and Kristensen paper (1992), it is likely it has less precision in its blood Pb estimates compared to all of the other papers evaluated; this may have contributed to its lack of finding for an association between blood Pb and cases of coronary heart disease (fatal and nonfatal).

Another limitation is that Møller and Kristensen (1992) do not provide data on the prevalence and intensity of smoking and drinking in the cohort. Since the authors note that "much of the mortality in this rather young cohort is due to alcohol-related causes of death, such as liver cirrhosis, pancreatitis and suicide in alcohol abusers," it seems likely that the cohort had high alcohol intakes. If the cohort examined had a large number of individuals who smoke and drink, this could attenuate the impact of any Pb exposure as it relates to CVD mortality.

The Weisskopf et al. (2009)[16] paper (described in Section 3.2.7) also failed to find an association between blood or bone Pb and CVD mortality. However, the results should be considered in light of the method of selection for the Normative Aging Study (NAS) cohort, which suffers from

---

[16] Note: the original study was published in 2009 but this summary is based on the correction to the study which was posted to *Circulation* (2014). The NTP Monograph and EPA ISA reviewed the uncorrected version of this paper.

selection bias and bias due to conditioning on an intermediate.[17] This is exemplified by the fact that in a reanalysis of the data in the NAS cohort, in which efforts were taken to mitigate biases, statistically significant positive associations were found between patella Pb and all-cause, CVD and ischemic heart disease related mortality (Weisskopf et al., 2015). However, even after the mitigation of bias in the Weisskopf et al. (2015) paper, a statistically significant association was not found between blood Pb and CVD mortality.

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. 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, the lack of association may be due to certain attributes of study populations in the cohorts (e.g., age, alcohol or tobacco use) or the lack of precision in the blood Pb estimates (in the case of Møller and Kristensen (1992)).

---

[17] Often referred to as over adjustment (Weisskopf et al., 2015). For example, "if one is interested in assessing the overall effect of an exposure on an outcome, it is not necessary to stratify, and indeed, it is important not to stratify, on an intermediate. Second, if one does condition on an intermediate, to try to obtain what might conceived of as a "direct effect" of the exposure on the outcome, then various biases and paradoxical results can arise. It is now well documented theoretically and empirically that, when there is an unmeasured common cause of the intermediate and the outcome, associations adjusted for the intermediate are subject to bias" (VanderWeele, Mumford, & Schisterman, 2012).