EPA/600/R-23/061
March 2023
www.epa.gov/isa

United States Environmental Protection Agency

# Integrated Science Assessment for Lead

## Appendix 5: Renal Effects

## External Review Draft

March 2023

Health and Environmental Effects Assessment Division
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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# DOCUMENT GUIDE

This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 12 appendices, which can all be found at https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=357282.

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# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| β2-MG | β2-microglobulin |
| AAS | angiotensin-aldosterone system |
| ACE | angiotensin-converting enzyme |
| ACR | albumin-to-creatinine ratio |
| ALB | albumin |
| AQCD | Air Quality Criteria Document |
| BLB | body lead burden |
| BLL | blood lead level |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CKiD | Chronic Kidney Disease in Children |
| d | day, days |
| DKD | diabetic kidney disease |
| EAF | electric arc furnace |
| EBE | early biological effect |
| EDTA | ethylenediaminetetraacetic acid |
| eGFR | estimated glomerular filtration rate |
| ESRD | end-stage renal disease |
| ETAAS | Electrothermal Atomic Absorption Spectrometry |
| EWAS | environment wide association study |
| F | female |
| FDR | false discovery rate |
| GFAAS | Graphite Furnace Atomic Absorption Spectrometry |
| GFR | glomerular filtration rate |
| GW | gestation week |
| HbA1c | hemoglobin A1c |
| HDL | high-density lipoprotein |
| hr | hour, hours |
| HR | hazard ratio |
| ICP-MS | Inductively Coupled Plasma Mass Spectrometry |
| IQR | interquartile ratio |
| ISA | Integrated Science Assessment |
| KIM-1 | Kidney Injury Molecule 1 |
| KNHANES | Korea National Health and Nutrition Examination Survey |
| KRIEFS | Korean Research Project on the Integrated Exposure Assessment to Hazardous Materials for Food Safety |
| MCDS | Malmö Cancer and Diet Study |
| MCDS-CC | cardiovascular cohort of the Malmö Cancer and Diet Study |
| MDRD | Modification of Diet in Kidney Disease |
| mo | months |
| M | male |
| M/F | male/female |
| MONICA | Monitory of Trends and Cardiovascular Disease |
| NAG | N-acetyl-β-D-glucosaminidase |
| NAS | Normative Aging Study |
| NGAL | neutrophil gelatinase-associated lipocalin |
| NHANES | National Health and Nutrition Examination Survey |
| $NO_3$ | nitrate |
| OR | odds ratio |
| Pb | lead |
| PbO | lead oxide |
| $Pb(NO_3)_2$ | lead nitrate |
| PECOS | Population, Exposure, Comparison, Outcome, and Study |
| PND | postnatal day |
| Q | quartile |
| RAAS | renin-angiotensin-aldosterone system |
| SD | standard deviation |
| SE | standard error |
| SES | socioeconomic status |
| SPHERL | Study for Promotion of Health in Recycling Lead |
| SUA | serum uric acid |
| T | tertile |
| UA | uric acid |
| wk | week, weeks |
| WHO | World Health Organization |
| yr | year, years |

# APPENDIX 5 RENAL EFFECTS

***Summary of Causality Determinations for Pb Exposure and Renal Effects***

This appendix characterizes the scientific evidence that supports causality determinations for lead (Pb) exposure and renal effects. The types of studies evaluated within this appendix are consistent with the overall scope of the ISA as detailed in the Process Appendix (see Section 12.4). In assessing the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in Table 12-5 of the Process Appendix (Section 12.6.1). More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this appendix supports the following causality conclusions:

| Outcome | Causality Determination |
|---|---|
| Reduced Kidney Function | Causal |

The Executive Summary, Integrated Synthesis, and all other appendices of this Pb ISA can be found at https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=357282.

## 5.1 Introduction and Summary of the 2013 Integrated Science Assessment

In the 2013 Lead Integrated Science Assessment U.S. EPA (2013) the epidemiologic and toxicological evidence was judged to be "suggestive of a causal relationship" between Pb exposures and reduced kidney function among adults. Prospective epidemiologic studies in adult men in the general population (Tsaih et al., 2004; Kim et al., 1996) supported the temporal relationship between Pb exposure and reduced kidney function at blood Pb levels (BLLs) ≤ 10 µg/dL. As indicated by the male cohort of the Normative Aging Study (NAS), Kim et al. (1996) noted an increase in serum creatinine with increasing BLLs. Similarly, Tsaih et al. (2004) indicated a 0.009 mg/dL (95% confidence interval [CI]: −0.0008, 0.0188) annual increase in serum creatinine over 10 years, with a one-unit increase in natural log-transformed tibia Pb. Similar findings were observed when considering patella Pb as well. These population-based prospective cohort studies showed a longitudinal association between BLLs and increases in serum creatinine after adjustment for key potential confounders. In an additional prospective study, higher baseline BLLs were associated with greater chronic kidney disease (CKD) progression over time (i.e., reduced estimated glomerular filtration rate [eGFR] −0.040 mL/min/1.73 $m^2$ [95% CI: −0.0072, −0.008]) in CKD patients (Yu et al., 2004). Re-examination of a study from the 2006 Pb Air Quality Criteria Document (AQCD) (U.S. EPA, 2006a) provided data to conclude that in a population with likely

higher past exposures to Pb, a 10-fold increase in concurrent blood Pb was associated with a decrease in estimated creatinine clearance and that a 3.5 μg/dL increase in blood Pb had the same negative impact on eGFR as did an increase of 4.7 years in age or 7 kg/m$^2$ in body mass index (Åkesson et al., 2005). Cross-sectional studies of the general adult population added support to the associations observed in prospective epidemiologic studies. The majority of cross-sectional studies reported associations between higher measures of Pb exposure and impaired renal function (Navas-Acien et al., 2009; Muntner et al., 2005; Muntner et al., 2003). Other studies in clinical trials of CKD patients treated with ethylenediaminetetraacetic acid (EDTA) chelation provide supportive results; however, these studies had uncertainties concerning small sample sizes and lack of researcher blinding.

With respect to the animal toxicology evidence, the 2013 Pb ISA noted that at BLLs > 30 μg/dL, there was clear evidence that Pb exposure caused changes to kidney morphology and function (Khalil-Manesh et al., 1992b; Khalil-Manesh et al., 1992a). Evidence for functional changes in animals following lower Pb exposures resulting in BLLs < 20 μg/dL was generally not available. At BLLs between 20 and 30 μg/dL, studies with various exposure scenarios and in various lifestages provided evidence for reduced kidney function measures (e.g., decreased creatinine clearance, increased serum creatinine, increased blood urea nitrogen [BUN]). In addition, previous reviews have clearly established that exposure to Pb can result in the production of reactive oxygen species and markers of inflammation in the blood or kidneys over a similar range of BLLs (see (U.S. EPA, 2013)).

However, there were important uncertainties identified in the 2013 Pb ISA. First, because epidemiologic studies report effects in adult populations with past Pb exposures that are likely higher, uncertainty exists as to the Pb exposure level, timing, frequency, and duration contributing to the associations observed with blood or bone Pb levels. Second, due to the kidney's role in removing toxins from the blood, it is plausible that reverse causality could explain the associations observed in epidemiologic studies. While the epidemiologic and animal toxicological studies mentioned above suggest that reverse causality does not contribute substantially to associations between higher BLLs and reduced kidney function, reverse causation remained a plausible hypothesis. Thus, this bidirectional relationship is possible and additional evidence was needed to fully elucidate the extent to which diminished kidney function may itself result in increased blood or bone Pb levels.

When considered as a whole, although there was evidence of impaired kidney function in some epidemiologic studies, as well as animal toxicological evidence of oxidative stress and impaired kidney function providing biological plausibility for those associations, important uncertainties remained. In particular, uncertainties related to the potential for reverse causality in epidemiologic studies and the lack of animal toxicological studies indicating impaired kidney function at lower BLLs were noted. As a result, the relationship between Pb exposure and reduced kidney function was judged to be suggestive of a causal relationship.

The following sections provide an overview of study inclusion criteria for this Appendix (Section 5.2), an evaluation of the health evidence published since the 2013 Pb ISA (Sections 5.3−5.8), a summary

of the biologically plausible pathways by which exposure to Pb could result in the health outcomes observed in epidemiologic studies (Section 5.9), a discussion of the causal determination for Pb exposure and renal effects (Section 5.10), tables providing toxicological and epidemiologic study-specific details (Section 5.11), and references (Section 5.12).

## 5.2 Scope

The scope of this appendix is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements define the objectives of the review and establish study inclusion criteria, thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies that were included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. With the exception of supporting evidence used to examine the biological plausibility of Pb-associated renal effects, recent studies were only included if they satisfied all of components of the following discipline-specific PECOS statements:

**Epidemiologic Studies:**

**Population:** Any human population, including specific populations or lifestages that might be at increased risk of a health effect;

**Exposure:** Exposure to Pb[2] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[3]; or intervention groups in randomized trials and quasi-experimental studies;

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

[2] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area that was of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[3] Studies that estimate Pb exposure by measuring Pb concentrations in $PM_{10}$ and $PM_{2.5}$ ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-$PM_{10}$ and Pb-$PM_{2.5}$ with BLLs are lacking.

**Comparison:** Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles);
**Outcome:** Renal effects including, but not limited to, renal function and CKD; and
**Study Design:** Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

**Experimental Studies:**
**Population:** Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages);
**Exposure:** Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below;[1,2]
**Comparators:** A concurrent control group exposed to vehicle-only treatment or untreated control;
**Outcomes:** Renal effects; and
**Study Design:** Controlled exposure studies of animals in vivo.

## 5.3 Renal Disease and Histology

The primary function of the kidneys is to filter waste from the body while maintaining appropriate levels of water and essential chemicals, such as electrolytes. Kidney disease occurs when kidney function becomes impaired and cannot perform these functions adequately. Section 5.3.1 evaluates the epidemiologic evidence for kidney disease and exposure to Pb. Kidney disease is often accompanied by changes in the structure of the kidney. For example, glomerular or tubular hypertrophy can be used as an indication of kidney dysfunction and disease. Similarly, changes in the number or morphology of renal tubules or podocytes can also be indicative of kidney disease. Thus, Section 5.3.2 presents the animal toxicological studies that have examined histological sections of kidneys for abnormalities and changes in structure following Pb exposure.

### 5.3.1 Epidemiologic Studies of Kidney Disease

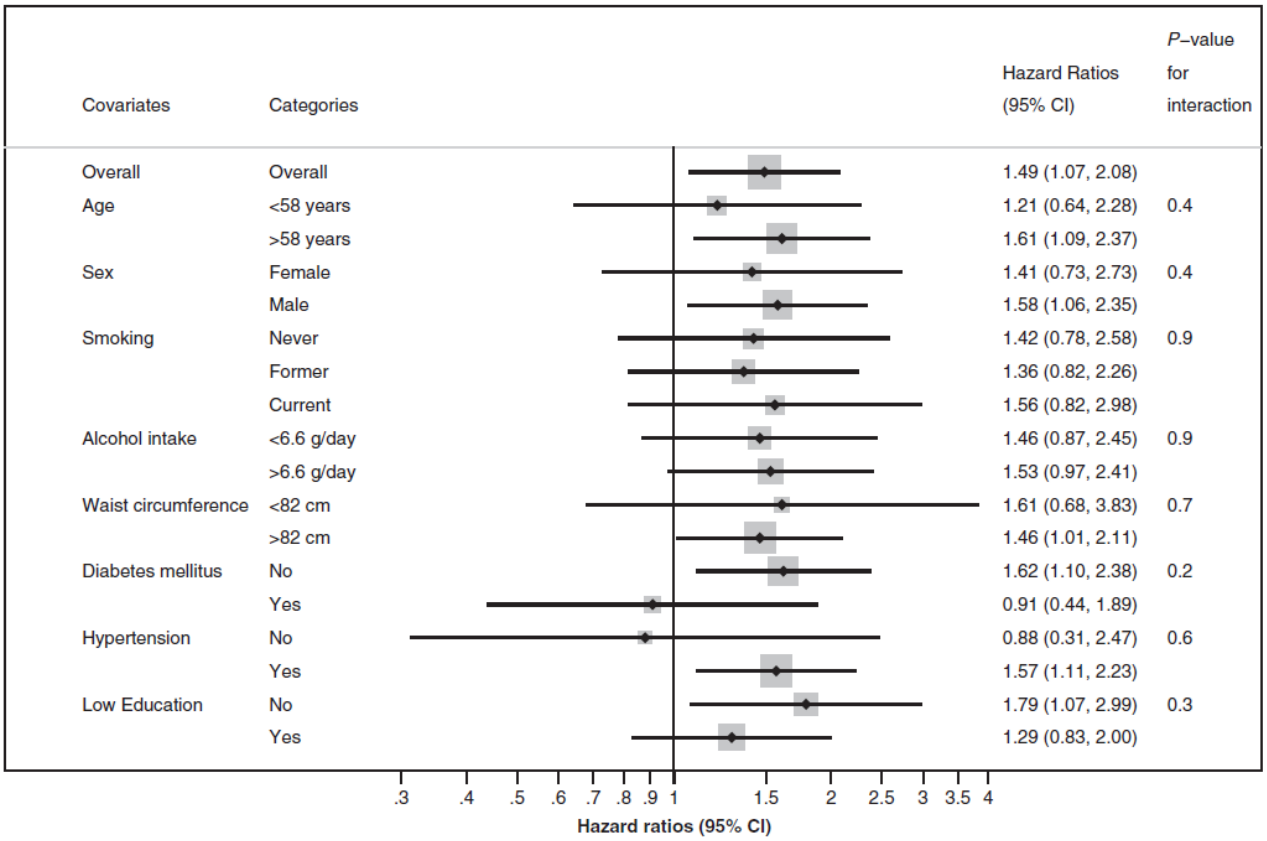
The 2013 Pb ISA (U.S. EPA, 2013) and 2006 Pb AQCD (U.S. EPA, 2006b) highlighted several studies indicating an association between biomarkers of Pb exposure and indicators of decreased renal function and progression of CKD. Several recent studies specifically evaluated biomarkers of reduced

[1] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[2] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

kidney function and the development of CKD or end-stage renal disease (ESRD). Study-specific details, including Pb biomarker levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 5-2. Study details in Table 5-2 include standardized results (kidney disease associated with a 1 μg/dL increase in BLL or a 10 μg/g increase in bone Pb level) as well as results that could not be standardized with the information provided in each paper.

#### 5.3.1.1 Chronic Kidney Disease

The 2013 Pb ISA presented a number of occupational studies evaluating the association between Pb exposure and CKD, but the results were relatively inconsistent. More recent evidence helps to disentangle the evidence previously presented and consistently indicates an association between biomarkers of Pb exposure and CKD development. A study among the cardiovascular cohort of the Malmö Cancer and Diet Study (MCDS-CC) in Malmö, Sweden evaluated the development of CKD by assessing baseline BLLs (obtained in 1991–1994) and incident CKD (assessed in 2007–2012) (Harari et al., 2018). In this study, CKD was confirmed through medical records. When each individual quartile of blood Pb was compared with the lowest, there was no association with incident CKD. However, when the three lower quartiles (Q1–Q3 median 2.2 μg/dL) were compared with the highest (Q4 median 4.6 μg/dL), an association was observed between blood Pb and CKD (hazard ratio [HR]: 1.49 [95% confidence interval (CI): 1.07, 2.08]), while controlling for baseline eGFR in the models. This association remained stable even after stratification by several covariates (Figure 5-1).




Cm = centimeters; g = grams.
Source: Harari et al. (2018).

**Figure 5–1 Modification of association between blood Pb (quartile 1–3 versus quartile 4) and chronic kidney disease incidence.**

A case-control study in Taiwan matched healthy controls by age and sex to those with CKD (Wu et al., 2019). In this study, CKD was defined as an eGFR < 60 mL/min/1.73 $m^2$ for at least 3 consecutive months. When compared with the lowest tertile (≤2.784 µg/dL) of blood Pb, the odds of CKD increased with each increasing tertile of red blood cell Pb. Compared with the lowest tertile, the highest tertile (>4.635 µg/dL) of blood Pb, was associated with an odds ratio (OR) of 6.48 (95% CI: 3.23, 12.99) for CKD. Since Pb can lead to oxidative damage in the kidney, the authors tested the association between red blood cell Pb and CKD modified by selenium. Selenium has antioxidant properties and selenium homeostasis is maintained by the kidney. When examined, serum selenium appeared to modify this association.

A large National Health and Nutrition Examination Survey (NHANES, 1999–2016) analysis included an environment wide association study (EWAS) on 262 environmental chemicals (Lee et al., 2020). Individual CKD components including albuminuria (urinary albumin [ALB]-to-creatinine ratio [ACR] ≥ 30 mg/g) and reduced eGFR (<60 mL/min/1.73 $m^2$ based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation) and a set of composite CKD measures were used as

outcome measures in this study. A discovery data set was created by combining five NHANES cycles (1999–2000, 2003–2004, 2007–2008, 2011–2012, and 2015–2016). Individual regression analyses were conducted for each survey cycle and combined using a random-effects meta-analysis. Chemicals with a false discovery rate (FDR) < 1% in the meta-analysis were considered as potential risk factors for CKD. Identified chemicals were then reanalyzed in the rest of the survey cycles (2001–2002, 2005–2006, 2009–2010, and 2013–2014) and referred to as the "validation" set. Blood Pb was analyzed in both the discovery and validation sets for reduced eGFR and the composite CKD definitions (the FDR for albuminuria was >1%). When assessing a composite CKD measurement (ACR ≥ 300 mg/g and eGFR <60 mL/min/1.73 $m^2$, ACR ≥ 30 mg/g and eGFR < 45 mL/min/1.73$m^2$ or eGFR < 30 mL/min/1.73 $m^2$), there was a positive association with blood Pb in the discovery (OR: 1.73 [95% CI: 1.54, 1.95]) and validation (OR: 1.61 [95% CI: 1.35, 1.90]) sets. In contrast, Kim et al. (2015) cross-sectionally evaluated the association between blood Pb and self-reported CKD using the Korea National Health and Nutrition Examination Survey (KNHANES 2011) and found a null association (OR: 1.05 [95% CI: 0.85, 1.30]) after controlling for confounders. The association remained null after stratifying by diabetic status.

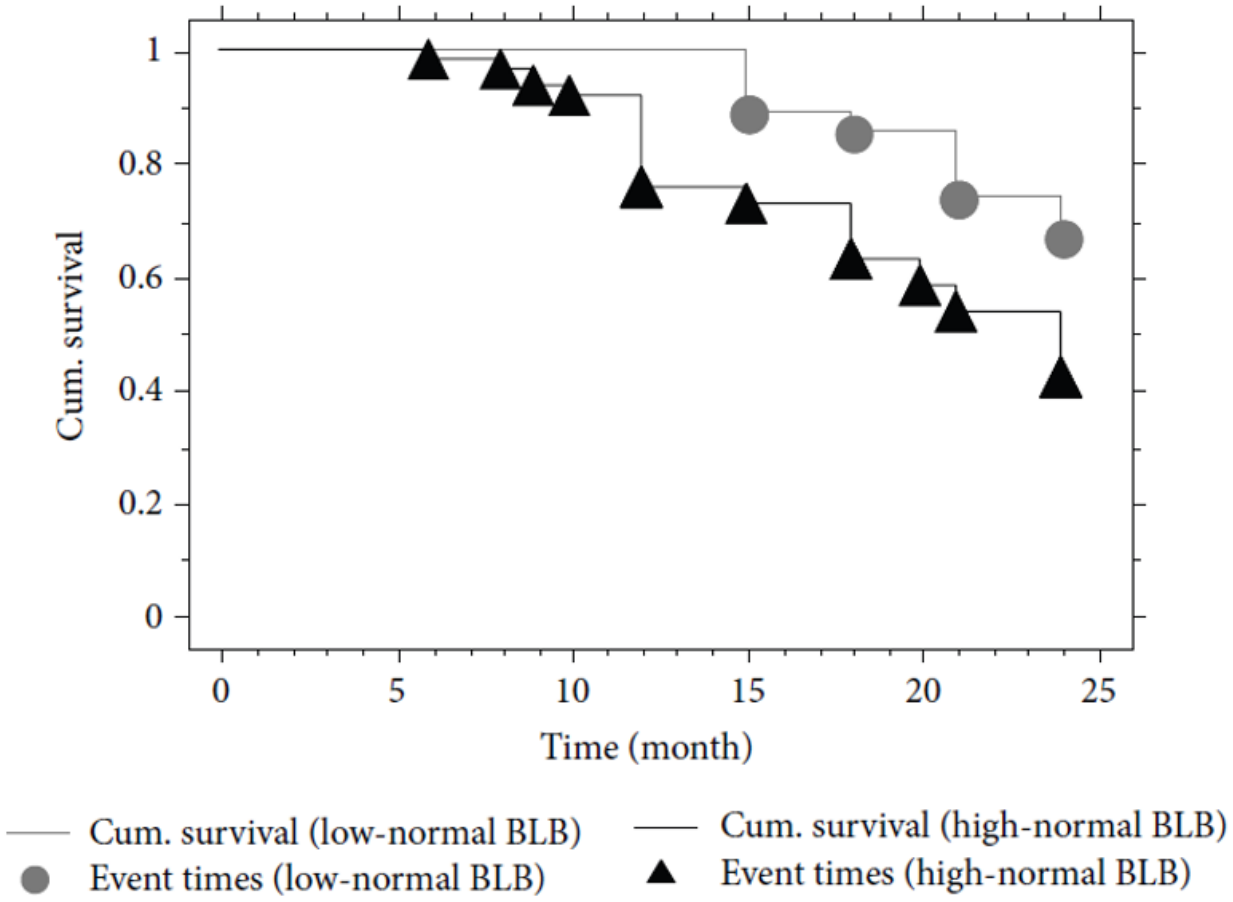
#### 5.3.1.2 End-Stage Renal Disease

ESRD is diagnosed when CKD progresses to a level in which renal replacement therapy (hemodialysis or transplantation) is required. Sommar et al. (2013) combined studies including the Northern Sweden Health and Disease Study and MCDS. The Northern Sweden Health and Disease Study incorporates data from three different cohorts: the Västerbotten Intervention Project, the Northern Sweden World Health Organization (WHO) Monitory of Trends and Cardiovascular Disease (MONICA) study, and Mammography Screening Project. All included studies collected baseline data on erythrocyte Pb levels. Cases of ESRD were identified through the Swedish Renal Registry and linked with erythrocyte Pb data from the above cohorts. Controls were selected from within each of the respective studies and were matched on age, sex, cohort, and time of sampling. In a combined cohort of over 130,000 individuals, 118 cases of ESRD were identified (with 378 controls). Here, a one-unit (µg/dL) increase in erythrocyte Pb was associated with an OR of 1.14 (95% CI: 1.03, 1.26).

#### 5.3.1.3 Diabetic Nephropathy

Diabetic nephropathy refers to a reduction in kidney function leading to ESRD among those with Type 1 or II diabetes mellitus. The development of ESRD or CKD is more likely among those with diabetes mellitus, compared with the general population. Huang et al. (2013) evaluated type 2 diabetics with stage 3 diabetic nephropathy (eGFR range: 30-60 mL/min/1.73 $m^2$). Body Pb burden (BLB) and blood Pb were assessed in this study. A combination of X-Ray fluorescence detecting bone Pb concentrations and calcium disodium EDTA demobilization tests are typically used to assess BLB. Typically, a BLB < 80 µg is considered to be within the normal range, while a BLB >600 µg is equivalent

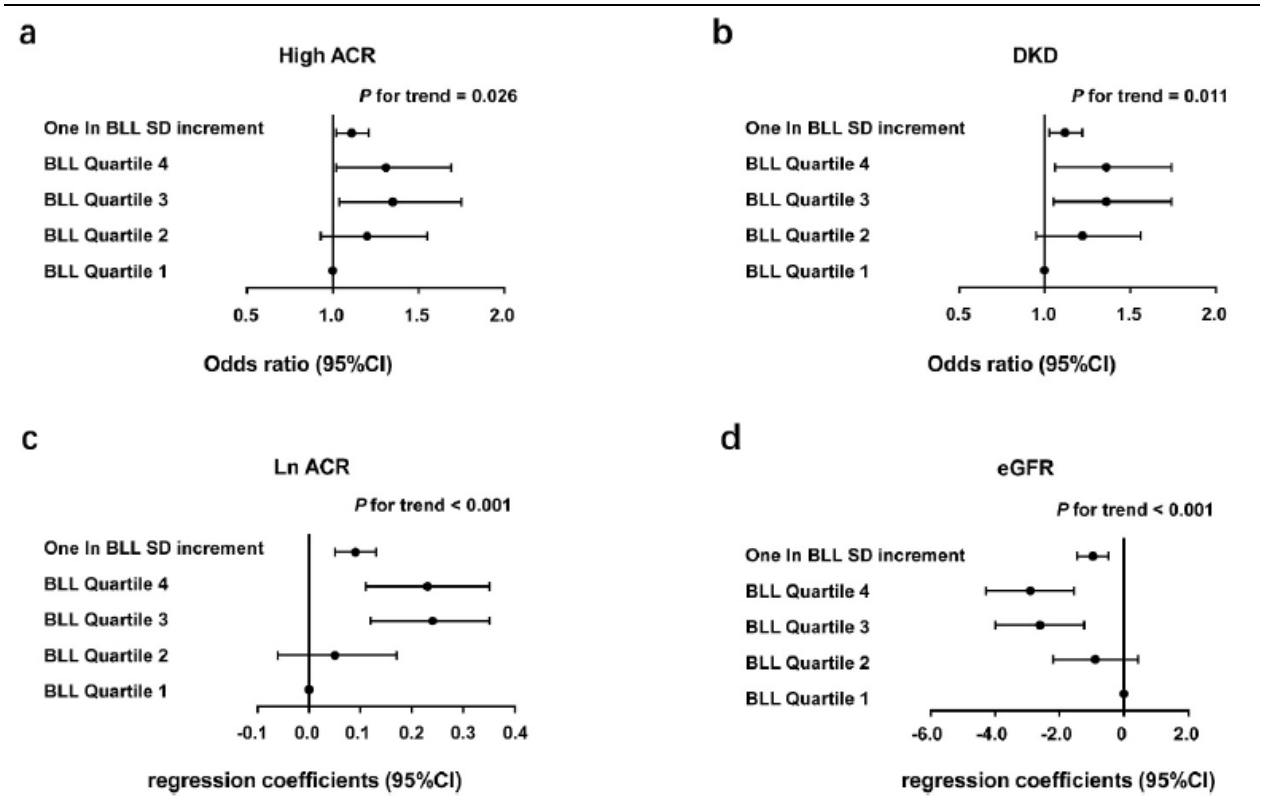
to Pb poisoning. This small study (n = 89) indicated a decrease in eGFR associated with a one-unit increase in either BLB (−0.022 mL/min/1.73 $m^2$ [95% CI: −0.039, −0.005]) or blood Pb (−0.298 mL/min/1.73 $m^2$ [95% CI: −0.525, −0.071]). Additionally, there was an increased risk of the "primary outcome" (either a two-fold increase in serum creatinine from baseline, the need for long-term hemodialysis, or death) with a one-unit increase in Pb BLB (HR: 1.01 [95% CI: 1.01, 1.02]), and a BLB between 80-600 µg was associated with an HR of 2.79 (95% CI: 1.25, 6.25). The Kaplan-Meier analysis conducted within this study demonstrated that diabetic patients with higher BLB (>80 µg) were more likely to reach the primary outcome at an accelerated rate compared with those with lower BLB (Figure 5-2).




BLB = body lead burden.
Source: Huang et al. (2013).

**Figure 5–2 Kaplan-Meier curve comparing low to high body Pb burden and the development of either a two-fold increase in serum creatinine from baseline, the need for long-term hemodialysis, or death among type 2 diabetics.**

A recent cross-sectional study evaluated diabetic kidney disease (DKD) in those with type 2 diabetes (Hagedoorn et al., 2020). The authors directly calculated GFR by measuring creatinine in a 24-hour urine sample, rather than calculating eGFR from a single serum creatinine measurement. In addition, the study also evaluated albuminuria, defined as a 24-hour urinary ALB excretion >30 mg/day. Each doubling of blood Pb (on a $\log_2$ scale) was associated with an OR of 1.83 (95% CI: 1.07, 3.15) for creatinine clearance < 60 mL/min/1.73 $m^2$ and an OR of 1.75 (95% CI: 1.11, 2.74) for albuminuria. Wan et al. (2021) cross-sectionally evaluated diabetic patients in China by evaluating the association between BLLs and both an ACR >30 mg/g and DKD (defined as ACR > 30 mg/g or eGFR < 60 mL/min/1.73 $m^2$). When comparing the highest quartile of blood Pb (≥3.7 µg/dL) with the lowest quartile of blood Pb (≤1.8 µg/dL), the odds of an elevated ACR (>30 mg/g) (OR: 1.31 [95% CI: 1.02, 1.69]) and the presence of DKD (OR: 1.36 [95% CI: 1.06, 1.74]) were higher. The dose response indicated increased odds of DKD with increasing blood Pb and a decrease in eGFR with each quartile increase in BLL (Figure 5-3).




ACR = albumin-to-creatinine ratio; BLL = blood lead level; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; SD = standard deviation.

Source: Wan et al. (2021).

**Figure 5–3 Association between blood Pb and renal outcomes among patients with type 2 diabetes.**

#### 5.3.1.4 Nephrolithiasis

Nephrolithiasis, or kidney stones, can be the result of a disruption in calcium homeostasis. Exposure to Pb, a nephrotoxicant, can potentially compete with calcium in binding to calcium-binding receptors, leading to the development of kidney stones. A prospective study evaluated baseline BLLs and the development of incident nephrolithiasis (verified by medical records) in a Flemish population as part of the Cadmium in Belgium (CadmiBel) study (Hara et al., 2016). Baseline blood Pb measurements were obtained between 1985 and 1989, and the incidence of nephrolithiasis was measured through October 2014. Approximately half of the population (747 out of 1302) had a second blood Pb measurement between 1991 and 2004. According to the baseline measurement, there was an increased risk of incident nephrolithiasis for each doubling of blood Pb (HR: 1.35 [95% CI: 1.06, 1.73]). A similar risk was noted when averaging the baseline and the follow-up BLLs (HR: 1.32 [95% CI: 1.03, 1.71]). Furthermore, applying an additional regression dilution bias correction increased the magnitude of the baseline association (HR: 1.44 [95% CI: 1.07, 1.93]). Conversely, an NHANES (2007–2016) analysis cross-sectionally assessed the association between the self-reported prevalence of kidney stones and BLLs (Sun et al., 2019). Compared with the lowest or referent group (blood Pb: 0.05 μg/dL), increasing blood Pb values corresponded to ORs indicative of a protective effect against kidney stones in this population, with the highest blood Pb group (>5 μg/dL) corresponding to an OR of 0.64 (95% CI: 0.46, 0.90). This association persisted even when stratifying by sex, ethnicity, and body mass index (BMI).

#### 5.3.1.5 Summary of Kidney Disease

The sections above present mostly positive associations between BLLs and some kidney diseases from epidemiologic studies. More specifically, all but a single epidemiologic study demonstrated a positive association between measures of body Pb and some measure of CKD (Lee et al., 2020; Wu et al., 2019; Harari et al., 2018), ESRD (Sommar et al., 2013), and diabetic nephropathy(Wan et al., 2021; Hagedoorn et al., 2020; Huang et al., 2013). However, evidence for an association between measures of Pb and nephrolithiasis (i.e., kidney stones) was limited to a couple of studies with conflicting results (Sun et al., 2019; Hara et al., 2016). Importantly, epidemiologic studies demonstrating positive associations between measures of Pb and kidney disease were conducted in a variety of geographical areas and in different study populations. Moreover, in general, these analyses also controlled for a number of potential confounders, thus increasing confidence in these associations.

### 5.3.2 Toxicological Studies of Kidney Histology

In previous Pb ISAs, some studies reported that exposure to Pb induced changes in renal structure. For example, Roncal et al. (2007) found that Pb increased tubulointerstitial injury and arteriolopathy in rats. The BLL in this study was 26 μg/dL. Moreover, Jabeen et al. (2010) reported that

Pb exposure (no specified BLL) decreased kidney cortical thickness, decreased the diameter of renal corpuscles, and increased renal tubular atrophy in mice. In contrast to these studies, Vyskočil et al. (1995) reported that Pb exposure to female rats resulting in a BLL of 36 μg/dL caused no change in kidney function or nephrotoxicity. More information on these and other studies examining renal effects following Pb exposure can be found in Table 4-28 of the 2013 Pb ISA (U.S. EPA, 2013).

A number of studies published since the 2013 Pb ISA with BLLs ≤ 30 μg/dL have examined kidney tissue for indications of abnormalities following Pb exposure by drinking water or gavage. Basgen and Sobin (2014) reported that in young mice, exposure to Pb leading to BLLs ranging from 2.74 μg/dL to 4.7 μg/dL resulted in a statically significant glomerular volume increase ($p < 0.05$), but similar numbers of podocytes and podocyte volume densities. At higher BLLs (11.7 μg/dL to 20.3 μg/dL), this change to kidney structure was not observed. With respect to glomerular components at lower BLLs, the authors reported a statistically significant effect ($p < 0.05$) on mesangial volume and capillary lumen volume, but not podocyte volume (Basgen and Sobin, 2014). Similarly, although control rats had a well-preserved nucleus and normal tubular and glomerular morphology, renal tubules from rats exposed to Pb (21.9 μg/dL BLL) had irregular cell shapes, changes in cell and nuclear sizes, and minimal amounts of cytoplasm (Alcaraz-Contreras et al., 2016). Cells from renal tubules also displayed a loss of apical microvilli (Alcaraz-Contreras et al., 2016). In an additional study, Pb exposure resulting in a BLL of ~12 μg/dL on postnatal day (PND) 21 and ~23 μg/dL on PND 30 resulted in a statistically significant decrease ($p = 0.01$) of 1-α-hydroxylase at PND 21, but not PND 30 by western blot relative to controls. These authors further noted that the western blot results were in agreement with immunohistochemistry on kidney cells. (Rahman et al., 2018). Shi et al. (2020) reported that kidney tissue from rats with a BLL of ~10.21 μg/dL displayed cellular debris, tubular dilation, glomerulus hypercellularity, and other signs of distress while control kidney tissue showed no major histopathological changes. In agreement with this study, Laamech et al. (2016) also reported that relative to control animals, Pb-treated mice with a BLL of 18 μg/dL displayed glomerular hypercellularity. Gao et al. (2020) similarly reported histopathological changes consistent with damage following Pb exposure in rats. In this study, the BLL was 10.6 μg/dL and the authors reported congestion and vasodilation of the renal interstitium and swelling of tubules in Pb-exposed animals while controls appeared to have normal kidney structure (Gao et al., 2020). Likewise, Li et al. (2017) reported hyperemic glomeruli, increased glomerular volume, and swelling of some renal tubular epithelial cells after Pb exposure resulting in an average BLL of ~30 μg/dL, while histological sections from the control mice were normal.

In addition to the drinking water and gavage studies described above, Andjelkovic et al. (2019) reported that Pb exposure (BLL ~30 μg/dL) resulted in acute passive kidney hyperemia, but no significant pathologic changes following gavage. Moreover, Carlson et al. (2018) reported that in mice, exposure to Pb by drinking water resulted in minor renal lesions that were similar to those in control mice (e.g., simple tubular hyperplasia) and that these lesions were not indicative of major systemic health problems. However, it is worth noting that the BLL in this study was only 2.89 μg/dL, and thus, extensive renal lesions may not be expected.

In addition to the analyses described above, recent studies have examined the effects of Pb after inhalation exposure. Following inhalation exposure to Pb-oxide nanoparticles for 6 weeks (resulting in ~14 μg/dL BLL), Dumková et al. (2017) reported minor changes in kidney appearance relative to some, but not all control mice. These changes were mainly areas of mild inflammation around the renal corpuscles and tubules. Similarly, ultrastructural analysis of the kidneys also revealed only minor differences between Pb-treated and control mice. However, these authors noted thicker lamina densa, and the average distance between endothelial cell and podocyte cytoplasmic membranes increased following Pb exposure (Dumková et al., 2017). In an additional study by the same author, Dumková et al. (2020a) used Pb nitrate nanoparticles and a longer inhalation time (11 weeks, resulting in a BLL of 8.5 μg/dL) and reported that there were obvious morphological changes in renal tubules when compared with control mice. Moreover, pedicles of podocytes were reported to be irregularly arranged or lost altogether. After a 5-week clearance period, Pb levels in the kidneys and blood declined substantially (BLL 1 μg/dL), and there was evidence of regeneration in tubular and glomerular kidney tissue. However, in another analysis by the same author, Dumková et al. (2020b) reported that an 11-week exposure with Pb-oxide nanoparticles resulted in no significant change in mouse kidney morphology when compared with controls with BLLs as high as 17 μg/dL. Thus, it is possible that exposure to different forms of Pb results in differing degrees of kidney damage, but additional studies would be needed to confirm this possibility.

When considered as a whole, substantial evidence exists from studies published since the last Pb ISA suggesting that exposures resulting in BLLs ≤ 30 μg/dL result in histological abnormalities in the kidneys. Moreover, these abnormalities were reported following all tested routes of Pb exposure (i.e., drinking water, gavage, and inhalation). Additional information on the experimental design of more recent renal histology studies can be found in Table 5-9.

#### 5.3.2.1 Summary of Kidney Histology Studies

Most animal toxicological studies demonstrate that exposure to Pb results in abnormalities or damage to kidney cells or tissue (see Section 5.3.2). Effects include changes in glomerular and nucleus morphology, as well as changes in the amount of cellular cytoplasm. Histological effects were also identified following both oral and inhalation exposures.

## 5.4 Glomerular Filtration Rate and Other Markers of Kidney Function

The gold standard for assessing kidney function involves measurement of the GFR through administration of an exogenous radionuclide or radiocontrast marker (e.g., 125I-iothalamate, iohexol) followed by timed sequential blood samples or, more recently, kidney imaging, to assess clearance through the kidneys. This procedure is invasive and time-consuming. Therefore, serum levels of

endogenous compounds are routinely used to estimate GFR in large epidemiologic studies and clinical settings. Creatinine is the most commonly measured endogenous compound; measures of urea (e.g., BUN) and uric acid (UA) have also been examined for this purpose. Increased serum concentration or decreased kidney clearance of these markers can indicate kidney dysfunction. The main limitation of endogenous compounds identified to date is that non-kidney factors impact their serum levels. Specifically, since creatinine is derived from creatinine in muscle, muscle mass and diet affect serum levels resulting in variations in different population subgroups (e.g., women and children compared with men) that are unrelated to kidney function. Measured creatinine clearance, involving measurement and comparison of creatinine in both serum and urine, can address this problem. However, measured creatinine clearance utilizes timed urine collections, traditionally over a 24-hour period, and the challenge of complete urine collection over an extended time period makes compliance difficult. Therefore, equations to estimate kidney filtration that utilize serum creatinine but also incorporate age, sex, race, and, in some cases, weight (in an attempt to adjust for differences in muscle mass) have been developed. Although these are imperfect surrogates for muscle mass, such equations are currently the preferred outcome assessment method.

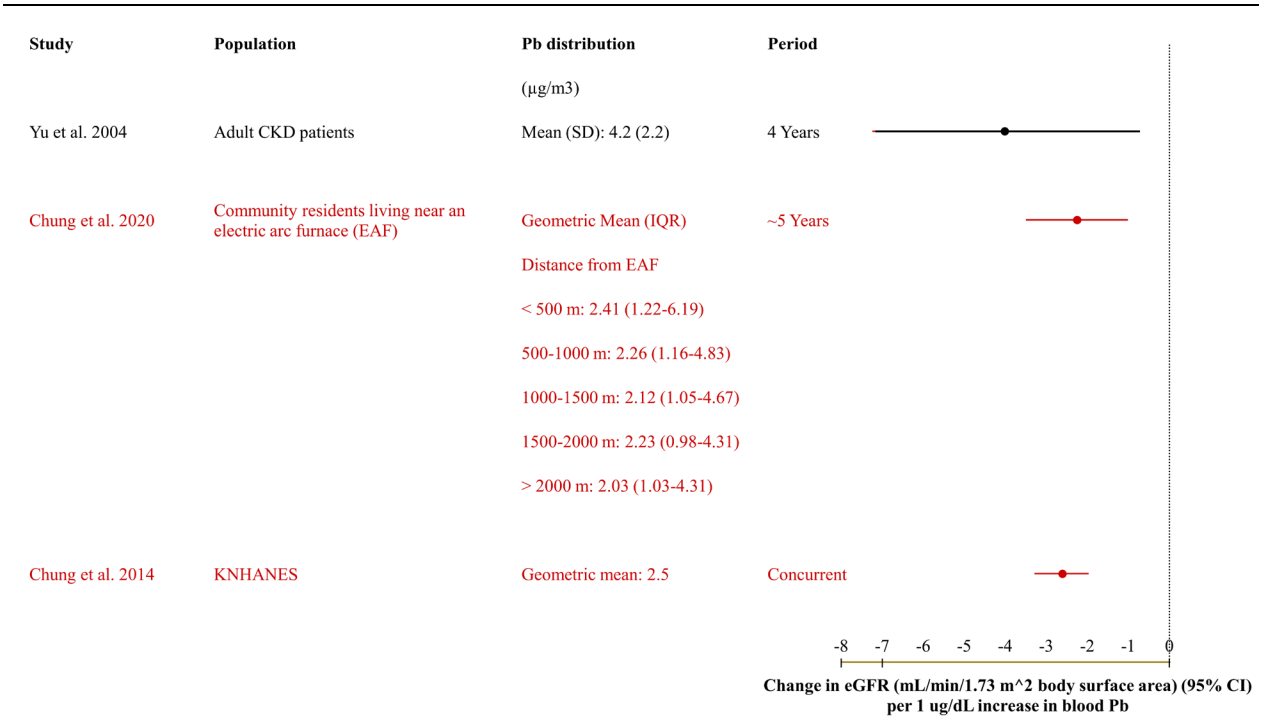
## 5.4.1 Glomerular Filtration Rate

### 5.4.1.1 Epidemiologic Studies of Estimated Glomerular Filtration Rate

Glomerular filtration rate can be estimated based on a variety of different biological factors and measured kidney function markers. An equation from the Modification of Diet in Kidney Disease (MDRD) Study (Levey et al., 2000; Levey et al., 1999) calculates eGFR based on serum creatinine, race, sex, and age. With widespread use of the MDRD equation, it became clear that the equation possibly underestimates GFR at high levels, even in the normal range. A second, creatinine-based equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), was recently developed in order to be more accurate than the MDRD equation, particularly at higher GFRs. This equation also incorporates serum creatinine, race, sex, and age. However, both equations do not consider an adjustment for muscle mass, therefore alternative biomarkers, such as cystatin C, a cysteine protease inhibitor that is filtered, reabsorbed, and catabolized in the kidney (Fried, 2009), have also been developed. The normal range of GFR is between 90 and 120 mL/min/1.73 $m^2$, and GFR < 60 mL/min/1.73 $m^2$ is typically indicative of kidney disease, while GFR < 15 mL/min/1.73 $m^2$ is a marker of renal failure.

The 2006 Pb AQCD (U.S. EPA, 2006b) and the 2013 Pb ISA (U.S. EPA, 2013) considered several studies that evaluated associations between biomarkers of Pb exposure and eGFR specifically in healthy adult populations as well as populations with comorbid conditions. Most studies indicated a relationship between Pb biomarkers and decreases in eGFR. Yu et al. (2004) studied eGFR (MDRD) among CKD patients in Taiwan and reported an association between blood Pb and an accelerated

decrease in eGFR. The 2013 Pb ISA (U.S. EPA, 2013) highlighted several cross-sectional studies that examined the association between BLLs and either eGFR or creatinine clearance. Navas-Acien et al. (2009) evaluated the association between BLLs and reduced eGFR (eGFR < 60 mL/min/1.73 m²) measured with the MDRD equation. This study reported reduced eGFR for the highest quartiles of blood Pb (>2.4 µg/dL), compared with the lowest (≤1.1 µg/dL). Several recent studies have also longitudinally and cross-sectionally evaluated the association between blood Pb and various measures of eGFR. Study-specific details, including BLLs, study population characteristics, confounders, and select results from these studies are highlighted in Figure 5-4 and Table 5-4. Studies in Figure 5-4 are standardized to be interpreted as changes in eGFR associated with a 1 µg/dL increase in BLL. Study details in Table 5-4 include standardized results as well as results that could not be standardized using the information provided in each paper.




CKD = chronic kidney disease.
Note: Studies published since the 2013 Pb ISA. Associations presented per 1 µg/dL increase in BLL.

**Figure 5–4 Associations between biomarkers of Pb exposure and estimated glomerular filtration rate.**

A recent analysis of the cardiovascular cohort of the Malmö Diet and Cancer Study (MDCS-CC) evaluated the change in eGFR from baseline to follow-up (Harari et al., 2018). Study participants were initially recruited between 1991 and 1994 (mean age: 57), when BLLs and eGFR (CKD-EPI) were initially assessed. Follow-up occurred between 2007 and 2012 (mean age: 73), when eGFR was re-

assessed. Compared with the lowest quartile of blood Pb (Q1: 0.15–1.85 µg/dL), eGFR was reduced in each of the higher quartiles. The highest quartile of blood Pb (3.3–25.8 µg/dL) was associated with a 2.3 mL/min/1.73 $m^2$ decrease (95% CI: −3.8, −0.73) in eGFR. Another recent longitudinal study of eGFR and BLLs was conducted in China (Liu et al., 2020). This study, among middle aged and older adults, evaluated the annual decline in eGFR (CKD-EPI) from baseline (2010) through the final follow-up (2013). Annual decline in eGFR was calculated as follows: Baseline eGFR – Follow-up eGFR)/Years of follow-up. Compared with the lowest quartile (<0.843 µg/dL) there was a 0.83 mL/min/1.73 $m^2$ (95% CI: 0.31, 1.35) decline in eGFR for those in the highest quartile (>1.895 µg/dL) per year. In addition, Chung et al. (2020) described a longitudinal cohort of those living near an electric arc furnace (EAF) in Taiwan. This study evaluated blood Pb assessed at baseline (measured in 2010–2011) and eGFR (method not specified; measured in 2015–2016). At follow-up, every 1 µg/dL increase in blood Pb was associated with a 2.25 mL/min/1.73 $m^2$ (95% CI: −3.50, −1.01) decrease in eGFR. A smaller prospective cohort study (BioCycle study) evaluated several kidney markers, including eGFR (MDRD) among premenopausal women in the United States (Pollack et al., 2015). The BioCycle study followed women for 2 menstrual cycles and included a total of 16 clinic visits (8 per cycle) timed to certain days of the menstrual cycle. Each doubling of blood Pb was associated with a −3.73% change in eGFR (95% CI: −6.55, −0.83). However, there was no association between a doubling of blood Pb and either eGFR < 90 mL/min/1.73 $m^2$ (OR: 0.32 [95% CI: 0.08, 1.21]), or < 60 mL/min/1.73 $m^2$ (OR: 0.32 [95% CI: 0.08, 1.21]).

Other studies evaluating biomarkers of Pb exposure and renal function were cross-sectional in nature. Cross-sectional studies can be useful for determining associations but are unable to establish the temporality of the association. Recently, the Study for Promotion of Health in Recycling Lead (SPHERL), a cross-sectional study evaluating newly hired Pb workers at battery manufacturing and Pb recycling plants in the United States, assessed blood Pb (taken at baseline, before large potential occupational exposure) and concurrent eGFR (CKD-EPI) (Mujaj et al., 2019). However, the SPHERL study only included men (n = 447) and indicated null associations with eGFR, whether using creatinine, cysteine C, or a combination of creatinine and cystatin C with increasing BLLs.

In addition, several nationally representative studies (KNHANES, NHANES) also evaluated the association between blood Pb and eGFR. Kim and Lee (2012) evaluated BLLs and eGFR (MDRD) cross-sectionally using KNHANES (2008–2010). Compared with the lowest quartile of blood Pb (Q1: ≤1.734 µg/dL), the highest quartile (Q4: >3.010 µg/dL) was associated with a 3.835 mL/min/1.73 $m^2$ decrease (95% CI: −5.730, −1.939) in eGFR. Similarly, increased odds of reduced eGFR (<80 mL/min/1.73 $m^2$) were observed when comparing Q4 with Q1 (OR: 1.631 (95% CI: 1.246, 2.136). In another KNHANES (2008) study, Chung et al. (2014) evaluated blood Pb and eGFR (CKD-EPI) among adults over 20 years old. In linear models, there was a 2.61 mL/min/1.73 $m^2$ decrease (95% CI: −3.29, −1.97) in eGFR for each unit increase in blood Pb. Additionally, increased odds of reduced eGFR (<60 mL/min/1.73 $m^2$) were observed when comparing the highest quartile of blood Pb (Q4 mean: 4.13 µg/dL) with the lowest (Q1 mean: 1.38 µg/dL). Buser et al. (2016) cross-sectionally evaluated the

relationship between blood Pb and eGFR (CKD-EPI) using NHANES (2007–2012). This study reported an average 2.67 mL/min/1.73 $m^2$ decrease (95% CI: −4.78, −0.56) in eGFR when comparing the highest quartile (Q4: >1.82 µg/dL) to the lowest quartile (Q1 ≤ 0.79 µg/dL) of blood Pb. Another large NHANES (2003–2014) analysis (Jain, 2019) evaluated BLLs and decreased kidney function (eGFR (CKD-EPI) < 60 mL/min/1.73 $m^2$). Participants with BLLs >2.15 µg/dL had greater odds (OR: 1.567 [95% CI: 1.346, 1.823]) of decreased kidney function compared with those with lower BLLs.

As described above, Lee et al. (2020) conducted an EWAS on 262 environmental chemicals using NHANES (1999–2016). Reduced eGFR (<60 mL/min/1.73 $m^2$, CKD-EPI) was assessed within this study. The discovery data set was created by combining five NHANES cycles (1999–2000, 2003–2004, 2007–2008, 2011–2012, and 2015–2016). Individual regression analyses were conducted for each survey cycle and combined using a random-effects meta-analysis. Identified chemicals were then reanalyzed in the rest of the survey cycles (2001–2002, 2005–2006, 2009–2010, and 2013–2014) and referred to as the 'validation' set. Blood Pb was analyzed in both the discovery and validation sets for reduced eGFR. Overall, the association between reduced eGFR and one standard deviation (SD) increase in the log-transformed blood Pb concentration was positive in both the discovery (OR: 1.30 [95% CI: 1.19, 1.42]) and validation (OR: 1.20 [95% CI: 1.10, 1.30]) sets.

#### 5.4.1.2 Toxicological Studies of Glomerular Filtration Rate

In the previous Pb ISAs, some studies found that exposure to Pb-induced changes in indicators of renal function and structure. For example, in a few studies by the same authors in rats (mean blood Pb ~30–45 µg/dL), decreases in GFR consistent with hyperfiltration and renal hypertrophy were reported (U.S. EPA, 2013). This is important given that kidney hyperfiltration can be seen in early-stage diabetes, and over time, can eventually lead to decreased kidney function. Since the publication of the document, Shi et al. (2020) reported that a 28-day Pb drinking water exposure in rats (BLL of ~10.21 µg/dL) resulted in a statistically significant decrease in GFR. Decreases is GFR are also important, potentially indicating progression of kidney disease and ultimately, kidney failure. Additional information on the experimental design of this toxicological study can be found in Table 5-5.

#### 5.4.1.3 Integrated Summary of Glomerular Filtration Rate

The 2006 Pb AQCD (U.S. EPA, 2006b) reported an association between BLLs and accelerated decreases in eGFR in CKD patients (Yu et al., 2004). Since the 2013 Pb ISA (U.S. EPA, 2013), longitudinal cohort studies have all reported an association between increases in BLLs and decreases in eGFR (Chung et al., 2020; Liu et al., 2020; Harari et al., 2018; Pollack et al., 2015). In agreement with these longitudinal studies, cross-sectional epidemiologic studies from the previous and current review generally reported positive associations between measures of blood or bone Pb concentrations and

decreased eGFR(Jain, 2019; Buser et al., 2016; Chung et al., 2014; Kim and Lee, 2012; Navas-Acien et al., 2009). In agreement with the majority of the epidemiologic evidence, an animal toxicological study reported that Pb-exposed rats had a statistically significantly lower ($p < 0.05$) GFR relative to control rats (Shi et al., 2020) (Section 5.4.1.2). When considered as a whole, there is clear evidence that exposure to Pb can result in a decrease in eGFR.

## 5.4.2 Albumin, Creatinine, and Albumin-to-Creatinine Ratio

### 5.4.2.1 Epidemiologic Studies of Albumin, Creatinine, and Albumin-to-Creatinine Ratio

Increased levels of creatinine in blood or serum, or decreased levels of these markers in urine can be indicative of impaired kidney function. The 2013 Pb ISA (U.S. EPA, 2013) noted positive associations between biomarkers of Pb exposure and serum creatinine. The ISA highlighted several longitudinal NAS studies (Tsaih et al., 2004; Kim et al., 1996) and cross-sectional analyses (Åkesson et al., 2005)that evaluated the effects of bone and blood Pb exposure on creatinine. Several of these analyses indicated positive associations between biomarkers of Pb exposure and increases in creatinine. Kim et al. (1996) conducted a sensitivity analysis that excluded a subset of the cohort with high past Pb exposures. The results among individuals with past Pb exposures (measured as early as 1979) ≤ 10 µg/dL were consistent with the results based on the entire cohort, suggesting that the association between blood Pb and increased serum creatinine is not heavily influenced by high past Pb exposures. In addition, increases in urinary ALB and ACR are also commonly used to assess kidney function. All of these measures can help indicate how well the kidney is functioning. Recent evidence continues to generally indicate an increased association between biomarkers of Pb exposure and increases in ALB, creatinine, and ACR. Study-specific details, including BLLs, study population characteristics, confounders, and select results from these studies are highlighted in Table 5-6. Study details in Table 5-6 include standardized results (ACR associated with a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level) as well as results that could not be standardized with the information provided in each paper.

The BioCycle study evaluated several different markers of kidney function, including eGFR (Section 5.4.1.1) and blood Pb among premenopausal women (Pollack et al., 2015). During the course of two menstrual cycles (8 weeks) there was a 3.47% increase (95% CI: 0.85, 6.16) in creatinine with each doubling of blood Pb. However, there was no associated increase in ALB (−0.38% [95% CI: −1.28, 0.52]) during the study period. This study also assessed several other biomarkers of kidney damage and indicated no further associations between blood Pb and kidney dysfunction. In an NHANES (2007–2012) analysis, Buser et al. (2016) evaluated urinary ALB. However, the study did not observe an association with urinary ALB and blood Pb (6.29 mg/g creatinine (95% CI: −6.39, 20.80) when comparing the highest quartile (Q4: >1.82 µg/dL) with the lowest quartile (Q1 ≤ 0.79 µg/dL) of blood Pb.

Mujaj et al. (2019) evaluated ACR within the SPHERL study. The SPHERL study was a cross-sectional analysis evaluating newly hired male Pb workers at battery manufacturing and Pb recycling plants in the United States and assessed blood Pb (taken at baseline, before large potential occupational exposure) and concurrent ACR. The authors indicated a null association between blood Pb and ACR (−0.071 mg/g (95% CI: −0.14, 0.59), among the men enrolled in the study. Jain (2019) also assessed decreased kidney function as ACR ≥ 30 mg/g (measure of albuminuria) among NHANES (2003–2014) participants. For those with BLLs >2.15 µg/dL, increased odds (OR: 1.206 [95% CI: 1.05, 1.385]) of ACR ≥ 30 mg/g creatinine were observed compared with those with lower BLLs. However, Zhu et al. (2019) evaluated blood Pb and ACR within another NHANES (2009–2012) cohort and reported a null association between quartiles of blood Pb and ACR.

In the EWAS study, described above, discovery and validation sets were created using NHANES (1999–2016) data on 262 environmental chemicals. In addition to other indicators, the authors also evaluated albuminuria (ACR ≥ 30 mg/g). In the discovery set, individual regression analyses were conducted for each survey cycle and combined using a random-effects meta-analysis. Chemicals with a FDR < 1% in the meta-analysis were considered as potential risk factors for CKD and reanalyzed in the validation set. Blood Pb was generally associated with albuminuria measured as ACR ≥ 30 mg/g, but the results were less consistent when the discovery set was compared with the validation set (discovery set: OR: 1.23 [95% CI: 1.07, 1.42], validation set: OR: 1.08 [95% CI: 0.97, 1.20]). However, when measured as ACR ≥ 300 mg/g, greater congruence was observed between the estimates (discovery set: OR: 1.39 [95% CI: 1.22, 1.59], validation set: OR: 1.38 [95% CI: 1.16, 1.63]).

#### 5.4.2.2 Toxicological Studies of Creatinine and Albumin

Previous Pb reviews included animal toxicological studies reporting that exposure to Pb increased serum levels of creatinine (see Table 4-28 in the 2013 Pb ISA). For example, Berrahal et al. (2011) reported that in rats with BLLs of 12.7 µg/dL and 7.5 µg/dL, serum creatinine levels were elevated. In addition, an animal toxicology study demonstrated increased urinary ALB following exposure to Pb (BLL of 20 µg/dL). Studies published since the 2013 Pb ISA are presented in sections 5.4.2.2.1 and 5.4.2.2.2 below. Moreover, additional information on the experimental design of toxicological studies of creatinine and ALB published since the 2013 Pb ISA can be found in Table 5-7.

##### 5.4.2.2.1 Creatinine

Since the publication of the 2013 Pb ISA, rodent toxicological studies have further demonstrated changes in creatinine levels following Pb exposure via drinking water or gavage. Zou et al. (2015) reported a statistically significant increase in serum levels of creatinine (BLL of 21.7 µg/dL) following a 30-day exposure in mice relative to controls. Similarly, Laamech et al. (2016) reported a statistically

significant increase in plasma levels of creatinine in 40-day Pb-treated animals (18 µg/dL BLL). In addition, Shi et al. (2020) reported that a 28-day Pb exposure in rats (BLL of ~10.21 µg/dL) resulted in a statistically significant increase in serum creatinine, as well as significantly ($p < 0.05$) lower urine creatinine (potentially indicating impaired kidney function). Following a single exposure in rats, (BLL of ~30 µg/dL), Andjelkovic et al. (2019) reported a small, but statistically significant increase ($p < 0.05$) in serum levels of creatinine. Finally, in kidney tissue, Gao et al. (2020) demonstrated a statistically significant decrease in creatinine activity following a 4-week Pb exposure (BLL of 10.6 µg/dL).

In addition to the drinking water and gavage studies mentioned above, a Pb nitrate nanoparticle inhalation study reported changes in creatinine levels. Following Pb nitrate nanoparticle inhalation for 11 weeks (but not 2 or 6 weeks, BLL at 11 weeks was 8.5 µg/dL), Dumková et al. (2020a) reported a statistically significant decrease in blood creatinine in mice. Notably, this inhalation study demonstrated a decrease in creatinine levels while the oral exposure studies mentioned above generally demonstrated an increase in these markers. Given this is a single inhalation study, it is difficult to deduce whether the result is repeatable, and if so, whether the difference is due to the route of exposure, the use of synthetic Pb particles, or another factor.

Finally, not all animal toxicological studies demonstrated changes in creatinine levels. Corsetti et al. (2017) reported no significant difference in serum creatinine levels following a 45-day Pb exposure (BLL 21.6 µg/dL) relative to control animals. Carlson et al. (2018) similarly reported that exposure to Pb resulting in a BLL of 2.89 µg/dL yielded creatinine levels that were not always within reference ranges but were not statistically different from the levels of control mice. Furthermore, in an analysis using Pb-oxide nanoparticles, and in contrast to their previous study (see (Dumková et al., 2020a) above), (Dumková et al., 2020b) observed no change in creatinine levels at 2, 6, or 11 weeks, potentially indicating a difference between Pb-oxide and Pb nitrate nanoparticle inhalation exposure (BLLs ranged from 10.4 to 17.4 µg/dL). It should be noted that creatinine levels were within reference ranges in both studies.

When the animal toxicological studies are considered together, there is evidence that exposure to Pb can result in changes in creatinine levels. Following drinking water or gavage exposure, most studies demonstrated an increase in serum creatinine levels, which could indicate impaired kidney function. However, it should be noted that a couple of these oral exposure studies, one of which was at a very low BLL (2.89 µg/dL), reported no change following Pb exposure. Results using Pb nanoparticle inhalation exposure were more variable, demonstrating either a decrease or no change in creatinine levels.

#### 5.4.2.2.2 Albumin

Since the publication of the 2013 Pb ISA, no animal toxicological studies have examined changes urinary ALB. Moreover, none of the existing studies demonstrated an increase in ALB serum or blood

levels. Studies either demonstrated no effect (Dumková et al., 2020a; Andjelkovic et al., 2019; Corsetti et al., 2017)or a decrease in ALB levels(Dumková et al., 2020b) following exposure to Pb.

#### 5.4.2.3 Integrated Summary of Creatinine and Albumin Levels

Increased levels of creatinine in blood or serum, or a decrease in urine, can be indicative of impaired kidney function. The 2013 ISA (U.S. EPA, 2013) included longitudinal epidemiologic studies that evaluated the effect of bone Pb exposure on serum creatinine levels (Tsaih et al., 2004; Kim et al., 1996). These studies both reported positive associations between increases in serum creatinine levels and bone Pb measurements. These results are in agreement with a more recent study in premenopausal women reporting a positive association between serum creatinine levels and increasing BLLs (Pollack et al., 2015).

Positive epidemiologic associations are supported by animal toxicological studies with BLLs below 30 µg/dL from both current and previous reviews. In particular, studies using oral exposures generally demonstrate higher creatinine levels in Pb-exposed animals when compared with controls (Shi et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2016; Zou et al., 2015; Berrahal et al., 2011; Roncal et al., 2007) (Section 5.4.2.2). However, more recent oral exposure studies demonstrated no change in serum creatinine levels in laboratory animals following Pb exposure (Carlson et al., 2018; Corsetti et al., 2017).

With respect to inhalation exposure to Pb (Dumková et al., 2020b) reported no change in creatinine levels. Nonetheless, it should be noted that Dumková et al. (2020b) was unique in that it used engineered Pb-oxide nanoparticles to expose mice via inhalation, rather than exposure through drinking water or ingestion as in other animal toxicological studies. Moreover, these results are in contrast to those from the same authors using Pb-nitrate nanoparticles, which reported a decrease in creatinine levels at similar time points (Dumková et al., 2020a). Thus, in animal toxicological studies, it is possible that the route of exposure or the type of Pb particles used (e.g., Pb-oxide versus Pb-nitrate) could influence serum creatinine levels. Nonetheless, the overall evidence indicates that exposure to Pb can produce increased levels of creatinine in blood or serum from both epidemiologic and animal toxicological studies. With respect to the levels of ALB, there is little evidence from epidemiologic or animal toxicological studies that exposure to Pb can increase serum, blood, or urine ALB levels.

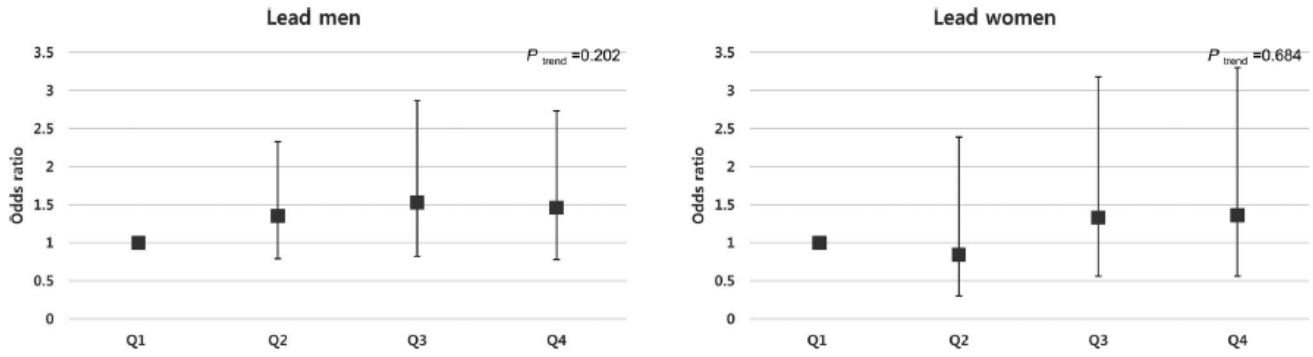
## 5.4.3 Uric Acid and Urea

### 5.4.3.1 Epidemiologic Studies of Uric Acid and Urea

UA is excreted in the urine and is the product of purine metabolism. Increased serum UA (SUA) levels can be indicative of reduced kidney excretion and is associated with multiple clinical outcomes including gout and CKD. Exposure to Pb is thought to alter UA homeostasis by effecting its kidney excretion (Emmerson and Ravenscroft, 1975) and increased UA can result in Pb-related nephrotoxicity (Weaver et al., 2005). Recent epidemiologic evidence supports an association between biomarkers of Pb exposure and increases in SUA. Study-specific details, including BLLs, study population characteristics, confounders, and select results from these studies are highlighted in Table 5-8. Study details in Table 5-8 could not be standardized (UA associated with a 1 μg/dL increase in blood Pb) with the information provided in each paper.

Park and Kim (2021) evaluated the association between blood Pb and SUA levels using KNHANES (2016–2017). This study noted an increase in SUA among women (0.019 mg/dL [95% CI: 0.001, 0.037 mg/dL]), but not men (−0.018 mg/dL [95% CI: −0.038, 0.002 mg/dL]) for each doubling of log-transformed blood Pb. This study also considered hyperuricemia (SUA levels ≥7 mg/dL in males or ≥6 mg/dL in females) but indicated null associations for both women and men. Arrebola et al. (2019) evaluated continuous SUA levels and the presence or absence of hyperuricemia (SUA levels ≥7 mg/dL in males or ≥6 mg/dL in females, SUA lowering medication use, or gout diagnosed by a physician) in the BIOAMBIENT.ES study. The study population had relatively low BLLs (median: 0.106 μg/dL). BLLs were not associated with SUA levels (0.01 ng/dL [95% CI: −0.02, 0.04 mg/dL]) or with hyperuricemia (OR: 1.12 [95% CI: 0.90, 1.41]). Another KNHANES analysis evaluated the effect between hyperuricemia (SUA levels ≥7 mg/dL in males or ≥6 mg/dL in females) and BLLs (Jung et al., 2019). This study also did not indicate an association between blood Pb and hyperuricemia (Figure 5-5).

Notably, no epidemiologic studies have examined the potential relationship between exposure to Pb and changes in measures of urea.




Adapted from: Jung et al. (2019).

**Figure 5–5 Association between blood Pb and hyperuricemia among men and women, Korea National Health and Nutrition Examination Survey, 2016.**

### 5.4.3.2 Animal Toxicological Studies of Uric Acid and Urea

Previous Pb reviews contained animal toxicological studies reporting that exposure to Pb increased serum levels of creatinine (see Table 4-28 in the 2013 Pb ISA). Roncal et al. (2007) demonstrated an increase in both serum UA and BUN following exposure to Pb (BLL 26 µg/dL). Similarly, Wang et al. (2010) demonstrated increased serum urea nitrogen levels following exposure to Pb. However, Pb levels were measured in serum, and thus the BLL was unknown. Studies published since the 2013 Pb ISA are presented in sections 5.4.3.2.1 and 5.4.3.2.2 below. Additional information on the experimental design of toxicological studies of UA and urea published since the 2013 Pb ISA can be found in Table 5-10.

#### 5.4.3.2.1 Uric Acid

Since the publication of the 2013 Pb ISA, Shi et al. (2020) reported that rats with a BLL of ~10.21 µg/dL had a statistically significant increase in UA relative to controls. However, Laamech et al. (2016) reported a statistically significant decrease (18 µg/dL BLL), and Andjelkovic et al. (2019) reported no change (~30 µg/dL BLL) in UA following exposure to Pb. Thus, there is limited evidence from animal toxicologic studies for increased levels of UA.

#### 5.4.3.2.2 Urea

Since the publication of the 2013 Pb ISA, rodent toxicological studies have further demonstrated changes in measures of urea following Pb exposure via drinking water or gavage. Zou et al. (2015)

reported a statistically significant increase in BUN (BLL of 21.7 µg/dL) following a 30-day exposure in mice relative to controls. Similarly, following exposure to Pb,Laamech et al. (2016) reported a statistically significant increase in plasma levels of urea (18 µg/dL BLL). In addition, Shi et al. (2020) reported that a 28-day Pb exposure in rats (BLL of ~10.21 µg/dL) resulted in a statistically significant increase in BUN. Similarly, in kidney tissue, Gao et al. (2020) demonstrated a statistically significant increase in BUN activity following a 4-week Pb exposure (BLL of 10.6 µg/dL). In contrast to studies that found an increase in serum BUN following Pb exposure, Andjelkovic et al. (2019) reported a statistically significant ($p < 0.05$) decrease in serum BUN (BLL of ~30 µg/dL). In addition, both Corsetti et al. (2017) (BLL 21.6 µg/dL) and Carlson et al. (2018) (BLL of 2.89 µg/dL) reported that exposure to Pb did not result in urea levels that were statistically different from those of control animals.

In addition to the studies above, a couple of Pb nanoparticle inhalation studies (by the same authors) reported mixed results. Following Pb nitrate nanoparticle inhalation for 11 weeks (but not 2 or 6 weeks; BLL at 11 weeks was 8.5 µg/dL), Dumková et al. (2020a) reported a statistically significant decrease in urea levels. However, in an analysis using Pb-oxide nanoparticles, no change in urea was reported at 2, 6, or 11 weeks (Dumková et al., 2020b), potentially indicating a difference between Pb-oxide and Pb nitrate nanoparticle inhalation exposure (BLLs ranged from 10.4 to 17.4 µg/dL).

The majority of the studies published since the last ISA indicate that oral exposure to Pb can result in changes in measures of urea (e.g., BUN). Most of these studies demonstrated an increase in serum urea levels, consistent with impaired kidney function. Inhalation studies conducted by the same laboratory were more variable, demonstrating no change or decreases in these markers. Additional information regarding the experimental designs of the of urea and UA studies included in this section can be found in Table 5-9.

#### 5.4.3.3 Integrated Summary of Uric Acid and Urea

Similar to other molecular markers that estimate kidney function, increased SUA, urea, and BUN levels can be indicative of impaired kidney function. Increased SUA levels are also associated with multiple clinical outcomes including gout and CKD. In an epidemiologic study, Park and Kim (2021) reported an increase in SUA among women, but not men. However, Arrebola et al. (2019) and Jung et al. (2019) reported that BLLs were not associated with either SUA levels or the presence of hyperuricemia. Animal toxicology studies were similarly mixed. Thus, there is limited evidence from epidemiologic and animal toxicological studies for increases in the levels of UA following Pb exposure.

With respect to measures of urea, some animal toxicological studies with mean blood Pb values ≤ 30 µg/dL have demonstrated a relationship between exposure to lead and increased serum BUN levels (Shi et al., 2020; Laamech et al., 2016; Zou et al., 2015). Similarly, Gao et al. (2020) demonstrated a statistically significant increase in kidney tissue BUN levels. Other oral exposure studies were mixed, either showing a decrease (Andjelkovic et al., 2019) or no effect (Carlson et al., 2018; Corsetti et al.,

2017). Inhalation studies by the same authors were also mixed, with some studies demonstrating a significant decrease in blood urea levels following inhalation of engineered Pb-nitrate (Dumková et al., 2020b) but not Pb-oxide nanoparticles(Dumková et al., 2020a) in rats. Some evidence from animal toxicology studies suggests that oral exposure can increase the levels of urea in blood following exposure to Pb.

### 5.4.4 Proteinuria and Hematuria

#### 5.4.4.1 Epidemiologic Studies of Proteinuria and Hematuria

Increased levels of protein (proteinuria) and blood cells (hematuria) in the urine can be markers of renal damage. Hematuria can either be benign or indicative of more serious outcomes including glomerulonephritis, CKD, kidney stones, or cancer. The 2013 Pb ISA (U.S. EPA, 2013) did not include any epidemiologic studies of proteinuria or hematuria. Study-specific details, including BLLs, study population characteristics, confounders, and select results from more recent studies examining these endpoints are highlighted in Table 5-10. Study details in Table 5-10 include standardized results (associated with a 1 μg/dL increase in BLL) as well as results that could not be standardized with the information provided in each paper.

Chung et al. (2014) evaluated the association between blood Pb and proteinuria using KNHANES (2008). Proteinuria was defined as ≥1 on a urine dipstick test (equivalent to ≥30 mg/dL). This study indicated that when compared with the lowest quartile (mean: 1.38 μg/dL), the odds of proteinuria (OR: 1.22 [95% CI: 1.00, 1.50]) were greater among participants in the highest quartile (mean: 4.13 μg/dL). Han et al. (2013) evaluated the association between hematuria (≥1 on urine dipstick test) and BLLs using KNHANES (2008–2010). A null association was observed when the highest quartile (Q4 >3.22 μg/dL) was compared with the lowest (Q1: <1.89 μg/dL) (OR: 0.78 [95% CI: 0.443, 1.361]).

#### 5.4.4.2 Toxicological Studies of Proteinuria and Hematuria

The previous ISA contained no evidence of proteinuria or hematuria from animal toxicological studies with reported BLLs. One study reported an increase in urinary protein levels but only measured Pb in serum Wang et al. (2010). No animal toxicological studies have been conducted with BLLs examining these outcomes since the 2013 Pb ISA. Thus, consistent with the epidemiologic studies presented above, there is only limited evidence for an effect of Pb on proteinuria and no evidence for an effect on hematuria.

#### 5.4.4.3 Integrated Summary of Proteinuria and Hematuria

There is little evidence from epidemiologic or animal toxicological studies that exposure to Pb results in proteinuria or hematuria

### 5.4.5 N-Acetyl-β-D-Glucosaminidase and $\beta_2$-Microglobulin

#### 5.4.5.1 Epidemiologic Studies of N-Acetyl-β-D-Glucosaminidase and $\beta_2$-Microglobulin

Many markers of kidney dysfunction may be insensitive for early detection of kidney damage. Recently, the development of early biological effect (EBE) markers of preclinical kidney damage has received substantial attention. Exposure to Pb is thought to directly affect the deterioration of tubular function, which can lead to the loss of essential divalent metals. The renal tubular biomarker N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme that is sensitive to renal impairment. Another renal tubular biomarker, $\beta_2$-microglobulin ($\beta_2$-MG), is typically reabsorbed through glomerular filtration. Increases in either NAG or $\beta_2$-MG correspond to damage to the renal tubules. Study-specific details, including BLLs, study population characteristics, confounders, and select results from these studies are highlighted in Table 5-11. Study details in Table 5-11 could not be standardized (associated with a 1 μg/dL increase in blood Pb) with the information provided in each paper.

Lim et al. (2016) evaluated the association between BLLs and both NAG and $\beta_2$-MG in the Korean Research Project on the Integrated Exposure Assessment to Hazardous Materials for Food Safety (KRIEFS). This study indicated null associations between log-transformed blood Pb and both NAG (0.09 units/g creatinine [95% CI: −0.05, 0.23 units/g creatinine]) and $\beta_2$-MG (0.01 μg/g creatinine [95% CI: −0.13, 0.15 μg/g creatinine]). Jung et al. (2016) also evaluated the association between blood Pb and NAG among participants residing near a cement plant in South Korea. There were null associations when high NAG levels (>5.67 U/L) were compared with low NAG levels between quartiles of blood Pb and NAG.

#### 5.4.5.2 Toxicological Studies of N-Acetyl-β-D-Glucosaminidase and $\beta_2$-Microglobulin

A study from the 2013 Pb ISA indicated an increase in β-2 microglobulin and N-acetyl-β-D-glucosaminidase following Pb exposure (Wang et al., 2010). However, this study only measured Pb levels in serum (serum Pb level: 20 μg/dL) and thus, the BLL is unknown. Similarly, Jayakumar et al. (2009)and Khalil-Manesh et al. (1992b) reported a change in N-acetyl-β-D-glucosaminidase following Pb exposure (BLLs and 45 μg/dL, and >55 μg/dL, respectively). Since the 2013 Pb ISA, no animal toxicological studies have been conducted with BLLs less than 30 μg/dL to examine these markers.

#### 5.4.5.3 Integrated Summary of N-Acetyl-β-D-Glucosaminidase and $\beta_2$-Microglobulin

Few epidemiologic studies have been conducted examining β-2 microglobulin and N-acetyl-β-D-glucosaminidase following Pb exposure, and these studies reported no association with BLLs. With respect to animal toxicological studies, a few studies from previous reviews demonstrated changes in N-acetyl-β-D-glucosaminidase following Pb exposure, but a couple of these studies were at BLLs >55 μg/dL. Thus, when considered together, epidemiologic and animal toxicological studies provide little evidence for an effect of Pb exposure on these markers at BLLs ≤ 30 μg/dL.

### 5.4.6 Toxicological Studies of Other Indicators of Kidney Function

In addition to the markers potentially indicating impaired kidney function discussed above, other markers have been examined in a small number of studies. Increases in total serum protein can also be indicative of impaired kidney function. However, Andjelkovic et al. (2019) reported no change in total serum protein following Pb exposure (BLL ~30 μg/dL). Moreover, other studies either reported no changes or decreases in total protein in blood at timepoints ranging from 2 weeks to 11 weeks following Pb nitrate (Dumková et al., 2020a) or Pb-oxide (Dumková et al., 2020b) nanoparticle inhalation exposure (BLLs ≤ 17.4 μg/dL in these studies).

Changes in the balance of metal ions in the kidney and blood can also be indicative of impaired kidney function. In particular, lower calcium levels can be indicative of kidney disease. Dumková et al. (2020a) reported a significant decrease in calcium levels in the kidney but not in blood following Pb nitrate nanoparticle inhalation for 2 weeks (but not 6 or 11 weeks when BLLs were higher; BLL at 2 weeks was 4 μg/dL). No changes in the blood levels of sodium or potassium were reported, but there was a statistically significant decrease in phosphorous levels in blood at 2 and 11 weeks (but not at 6 weeks). In an additional analysis using Pb-oxide nanoparticles, Dumková et al. (2020b) reported a statistically significant decrease in kidney calcium levels after 2 and 6 weeks, but not after 11 weeks of exposure (BLLs: 10.4 μg/dL at 2 weeks, 14.8 μg/dL at 6 weeks and 17.4 μg/dL at 11 weeks). In addition, this study found no changes in sodium or potassium levels in the kidney at any time point. There were also no changes in calcium, potassium, or sodium levels in the blood. Moreover, Andjelkovic et al. (2019) reported: 1) a statistically significant decrease in serum calcium and iron; 2) no change in blood copper, zinc, or phosphorus levels; and 3) a decrease ($p < 0.05$) in kidney tissue zinc, but not copper following Pb exposure (BLL ~30 μg/dL). Finally, Zou et al. (2015) reported no change in zinc levels but a decrease in iron levels in blood relative to control animals. When considered as a whole, there is limited evidence for changes in calcium and other ion levels in blood or tissue following exposure to Pb. Additional information on the experimental design of toxicological studies presented in this section can be found in Table 5-12.

## 5.5 Toxicological Studies of Metal Co-Exposures with Pb

A limited number of studies evaluated the effect of Pb on the kidney in conjunction with exposure to other metals. Andjelkovic et al. (2019) evaluated the effect of Pb exposure in combination with cadmium. Although the levels of creatinine, BUN, and UA were similar following co-exposure with cadmium, total serum protein and ALB levels were statistically lower than controls following co-exposure. In an additional study, Zou et al. (2015) reported a statistically significant increase in serum levels of creatinine and BUN following co-exposure of Pb and zinc, but the levels of these markers were lower than the levels following exposure to Pb alone.

With respect to metal ions and co-exposure, Andjelkovic et al. (2019) reported that co-exposure of Pb with cadmium resulted in a statistically significant decrease ($p < 0.05$) in the levels of zinc (but did not exacerbate the decrease compared with Pb alone) and no change in copper ion levels (similar to Pb alone) in kidney tissue. However, co-exposure with cadmium did result in a greater decrease in serum calcium, iron, and blood copper levels, but not zinc blood levels when compared with exposure to Pb alone. In addition, Zou et al. (2015) reported that co-exposure with zinc significantly increased blood iron levels relative to Pb exposure alone.

Overall, only a few studies have examined the potential effects of metal co-exposure on kidney-related endpoints. Moreover, these studies varied in their co-exposure metals and outcome assessments. Thus, it is difficult to draw conclusions on the effects of metal co-exposure with Pb on either markers of kidney function or ion concentrations.

## 5.6 Activation of Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of blood pressure and kidney homeostasis. For example, angiotensin II (Ang II) stimulates arteriolar vasoconstriction, leading to increases in blood pressure or hypertension. Angiotensin-converting enzyme (ACE) is involved in the activation of Ang II. The 2013 Pb ISA stated that vascular reactivity to Ang II increased following Pb exposure (Robles et al., 2007). In addition, exposure to Pb resulted in increases in kidney or serum ACE activity and renal Ang II-positive cells (Rodríguez-Iturbe et al., 2005; Sharifi et al., 2004; Carmignani et al., 1999). Moreover, use of an ACE inhibitor or blocking the Ang II receptor type 1 (AT-1) ameliorated Pb-induced increases in blood pressure (Simões et al., 2011). Since the 2013 Pb ISA, Fioresi et al. (2014) reported no change in ACE activity in plasma and cardiac tissue. Taken together, there is some evidence from older studies to suggest that exposure to Pb can result in changes in RAAS. Additional information on the study design of Fioresi et al. (2014) can be found in Table 5-12.

## 5.7 Renal Outcomes Among Children

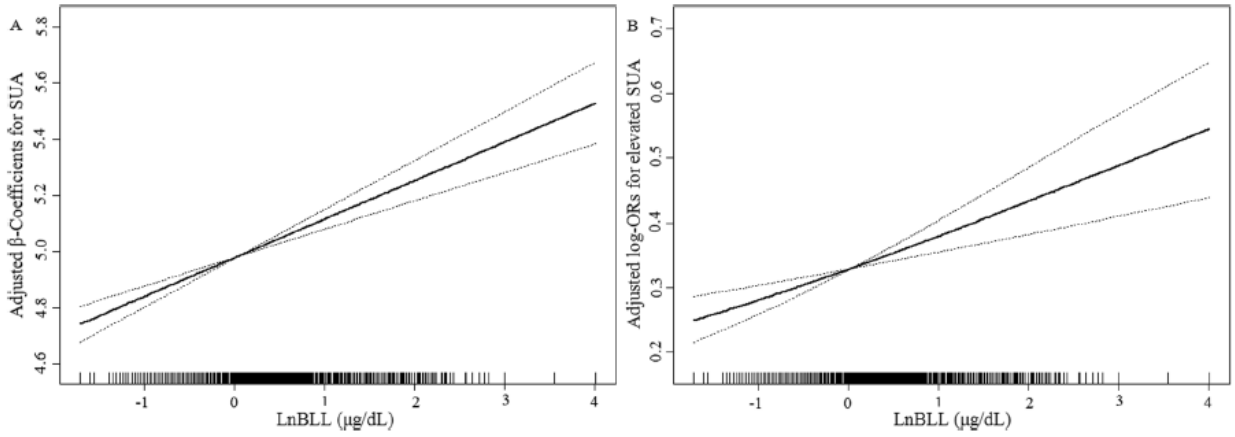
The 2013 Pb ISA (U.S. EPA, 2013) and 2006 Pb AQCD (U.S. EPA, 2006b) highlighted several studies indicating a lack of association between biomarkers of Pb exposure and renal outcomes among children. Many studies presented previously were among children with high exposures to Pb. Fadrowski et al. (2010) conducted an NHANES analysis that evaluated relatively low blood Pb values (median: 1.5 µg/dL) and two different measures of eGFR (cystatin C-based and creatinine-based). This study indicated an increase in eGFR based on an association between cystatin C and the highest quartile (>2.6 µg/dL) compared with the lowest (<1 µg/dL). More recent analyses not only continue to evaluate children with low BLLs, but also use techniques to more accurately measure GFR (either directly or an estimate) in children. Study-specific details, including Pb biomarker levels, study population characteristics, confounders, and select results from these studies are highlighted in Table 5-13. Study details in Table 5-13 include standardized results (associated with a 1 µg/dL increase in BLL) as well as results that could not be standardized with the information provided in each paper.

A recent longitudinal analysis evaluated the association between the erythrocyte fraction of Pb (Ery-Pb) in maternal blood and subsequent measurements of renal function, including kidney volume, eGFR (calculated based on serum cystatin C and deemed appropriate for use in children), and serum cystatin C, among children (~ 4.5 years) (Skröder et al., 2016). The Ery-Pb was assessed at both 14 weeks (GW14) and 30 weeks (GW30) of gestation. Linear regression analyses identified an association between decreased kidney volume and maternal Ery-Pb at 30 weeks of gestation (−0.071 $cm^3/m^2$ [95% CI: −1.4, −0.030]), but not at 14 weeks of gestation (−0.061 $cm^3/m^2$ [95% CI: −0.36, 0.24]). When stratified by sex, this association was stronger among girls (−1.1 $cm^3/m^2$ [95% CI: −2.1, −0.049]) than among boys (−0.80 $cm^3/m^2$ [95% CI: −1.80, 0.20]), for each 10 µg/kg increase in Ery-Pb. However, no differences in effect were observed when this outcome was stratified by birthweight or by children with stunted height. When considering other markers of renal dysfunction, no associations were present for eGFR (GW14 0.089 mL/min/1.73 $m^2$ [95% CI: −0.012, 0.30]; GW30 0.71 mL/min/1.73 $m^2$ [95% CI: −0.24,0.17]) or serum cystatin C (GW14 −0.00088 mg/L [95% CI: −0.0028, 0.001]; GW30 0.000027 [95% CI: −0.0018, 0.0018]).

Fadrowski et al. (2013) conducted a cross-sectional study evaluating children (aged 1–16) with CKD who were part of the Chronic Kidney Disease in Children (CKiD) prospective study. This study measured GFR directly by measuring the plasma disappearance inhexol curves (children had blood draws at 10, 20, 120, and 300 minutes after an injection of inhexol). The average percent change in GFR within the study was −2.1% (95% CI: −6.0, 1.8) for a 1 µg/dL increase in blood Pb. In the pediatric population, there are two main diagnoses for CKD: glomerular and nonglomerular. Glomerular CKD diagnoses include focal segmental glomerulosclerosis, hemolytic uremic syndrome, and systemic immunological diseases (systemic lupus erythematosus), whereas nonglomerular CKD includes aplastic/hypoplastic/dysplastic kidneys, reflux nephropathy, obstructive uropathy, and congenital urologic disease. Generally, nonglomerular CKD has an earlier onset and a slower rate of disease progression

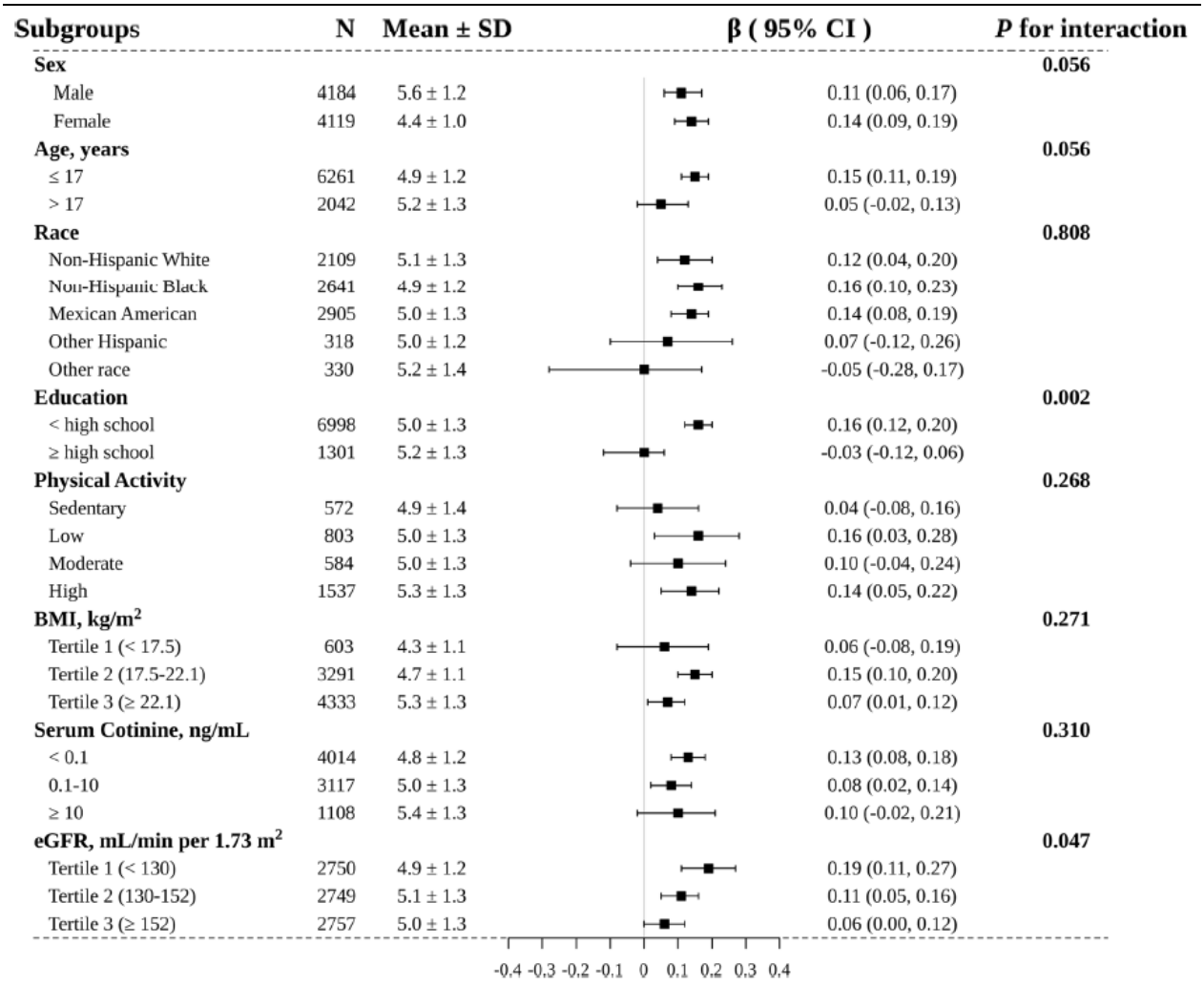
(Hooper et al., 2021). When stratified by the type of CKD (glomerular versus nonglomerular), children with glomerular CKD experienced a −12.1% change (95% CI: −22.2, −1.9) in GFR, compared with a −0.7% change (95% CI: −4.8, 3.4) among those with nonglomerular CKD. In another cross-sectional analysis, Cárdenas-González et al. (2016) evaluated BLLs and two biomarkers of kidney injury (Kidney Injury Molecule 1 [KIM-1] and neutrophil gelatinase-associated lipocalin [NGAL]) among Mexican children living in an area with a high prevalence of CKD. This study indicated null associations between blood Pb and biomarkers of kidney injury (results not shown).

An NHANES (1999–2006) analysis evaluated blood Pb and SUA among adolescents aged 12–19 (Hu et al., 2019). This study considered several confounders related to sociodemographic factors, blood biochemistry markers, and dietary intake. Overall, a one-unit increase in natural log (ln)-transformed blood Pb was associated with a 0.14 mg/dL (95% CI: 0.10, 0.17) increase in SUA. Additionally, the magnitude of the association was larger when examining elevated SUA (>5.5 mg/dL) and a one-unit increase in ln-transformed blood Pb (OR: 1.29 [95% CI: 1.17, 1.42]). Moreover, a restricted cubic spline analysis indicated a linear dose-response relationship between ln-transformed blood Pb and both continuous SUA and elevated SUA (>5.5 mg/dL) (Figure 5-6). Additionally, Hu et al. (2019) evaluated several of the model covariates (e.g., sex, race, and eGFR) in a subgroup analysis. The comparisons for these are shown in Figure 5-7. The authors reported that there were generally no interactions between blood Pb and other adjusted variables, except for educational attainment. Thus, the positive association remained, regardless of subgrouping.




BLL = blood lead level; dL = deciliter; µg = micrograms; Ln = natural logarithm; OR = odds ratio.
Source: Hu et al. (2019).

**Figure 5–6 Associations between natural log-transformed blood Pb (0–4 µg/dL) and serum uric acid and elevated serum uric acid (>5.5 mg/g).**




BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; kg = kilograms; m = meters; min = minute; mL = milliliter; ng = nanograms; SD = standard deviation.

Source: Hu et al. (2019).

**Figure 5–7 Subgroup analysis between blood Pb and serum uric acid among adolescents, National Health and Nutrition Examination Survey 1999–2006.**

### 5.7.1 Summary of Renal Outcomes Among Children

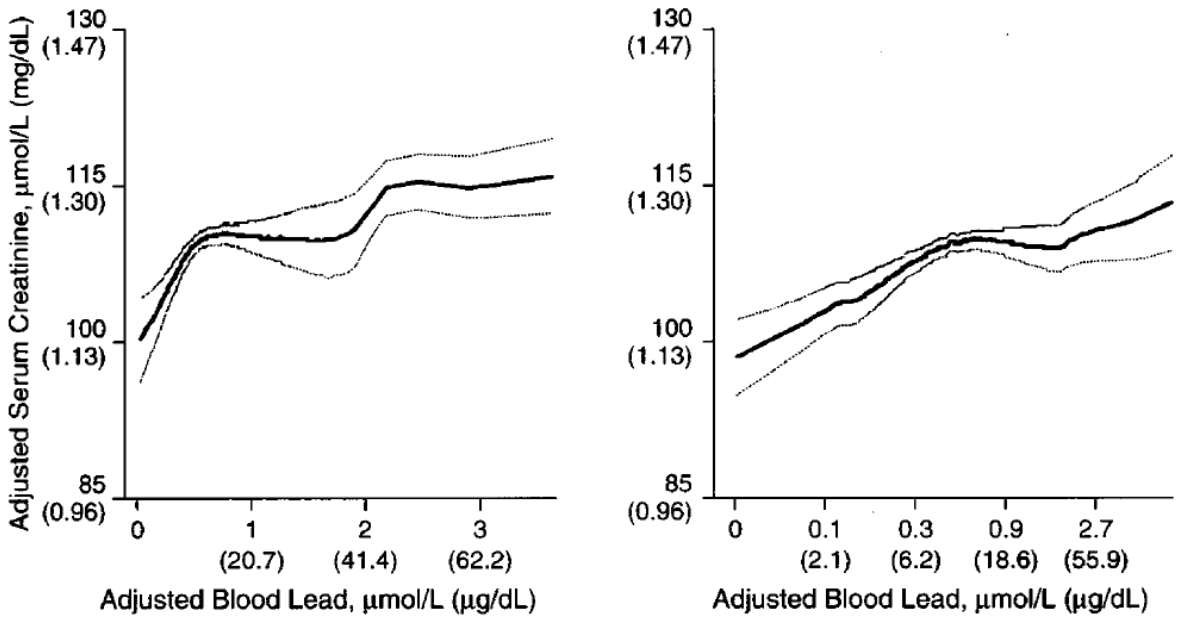
Skröder, 2016, 4685762@@author-year} conducted a longitudinal analysis evaluating the association between the erythrocyte fraction of Pb (Ery-Pb) in maternal blood and subsequent measurements of renal function among children (~ 4.5 years). The Ery-Pb was assessed at both 14 weeks (GW14) and 30 weeks (GW30) of gestation. Linear regression analyses identified an association between decreased kidney volume and maternal Ery-Pb at 30 weeks of gestation, but not at 14 weeks. No associations were present with eGFR or serum cystatin C. In addition, an NHANES (1999–2006) analysis

evaluated blood Pb and serum SUA among adolescents aged 12–19 taking into account several confounders related to sociodemographic factors, blood biochemistry markers, and dietary intake. Overall, there was a positive association between a one-unit increase in transformed blood Pb and continuous and elevated SUA (Hu et al., 2019). This study also evaluated several of the model covariates (e.g., sex, race, and eGFR) in a subgroup analysis, and no interaction was reported between blood Pb and other adjusted variables, except for educational attainment. In addition to these studies, a cross-sectional study evaluated children (aged 1–16) with CKD and measured GFR directly by measuring the plasma disappearance inhexol curves. Overall, this study did not indicate an association between blood Pb and GFR, except among those with a specific type (glomerular) of CKD (Fadrowski et al., 2013). Similarly, an additional cross-sectional analysis did not report an association between BLLs and biomarkers of kidney function among Mexican children living in an area with a high prevalence of CKD (Cárdenas-González et al., 2016). Taken together, there is limited evidence for an effect between biomarkers of Pb exposure and renal outcomes among children.

## 5.8 Reverse Causality

In observational research, reverse causality occurs when an association between an exposure and outcome is explained by the outcome that causes or alters the exposure. Reverse causality is a potential concern in studies of kidney function due to the role of the renal system in the excretion of toxins from the blood. Specifically, increased BLLs could result from reduced excretion due to kidney damage rather than as a causative factor for kidney impairment. The potential for reverse causality in epidemiologic studies is especially plausible in cross-sectional studies and studies conducted in study populations that are already experiencing renal dysfunction. In contrast, prospective analyses that include baseline measurements of biomarkers of Pb exposure and incident changes in renal function may help control for the possibility of reverse causality.

The 2006 Pb AQCD (U.S. EPA, 2006b) presented a longitudinal NAS study by Kim et al. (1996) where positive associations between BLLs and serum creatinine were reported over most of the range of serum creatinine (Figure 5-8). In locally weighted regression models, these associations were observed within the normal creatinine range, where reduced excretion of Pb is a less likely explanation of the observed association. A follow-up to this study evaluated the association between blood and bone Pb levels and serum creatinine among those with serum creatinine <1.5 mg/dL (Tsaih et al., 2004). This study indicated that the longitudinal associations did not materially change, suggesting that Pb dose contributed to renal dysfunction.




Source: Kim et al. (1996).

**Figure 5–8 Locally weighted smoothing plot of adjusted associations between blood Pb levels (with [left panel] and without [right paned] logarithmic transformation) and serum creatinine.**

The use of eGFR provides a better estimate of progressive changes in renal function than creatinine clearance. In a longitudinal study evaluated in the 2013 Pb ISA, Yu et al. (2004) indicated that baseline BLLs were associated with a decline in eGFR among CKD patients. More recent longitudinal analyses assessed changes in eGFR (Chung et al., 2020; Liu et al., 2020; Harari et al., 2018; Pollack et al., 2015) among a variety of populations free of kidney disease at baseline. Notably, in a population-based cohort study with an extensive follow-up period (Baseline: 1991-1994, Follow-up: 2007-2012), Harari et al. (2018) reported that increased baseline BLLs were associated with substantial decreases in eGFR from baseline. Since this study also adjusted for baseline eGFR, the larger decreases in kidney function observed in participants with higher Pb exposures ostensibly occurred in participants with similar baseline kidney function. Smaller cohort studies further supported this study by noting decreases in eGFR with increased BLLs (Chung et al., 2020; Liu et al., 2020; Pollack et al., 2015).

Furthermore, several recent epidemiologic studies evaluated the association between BLLs and the development of CKD or ESRD. In a population-based cohort in Sweden that showed Pb-related reductions in eGFR, Harari et al. (2018) also observed a relationship between BLLs at baseline and incident CKD after further adjustment for baseline eGFR. Additionally, a comprehensive analysis by Sommar et al. (2013) involved a combination of several existing cohort studies and subsequently linked incident ESRD cases to members of the cohorts. This study identified a modest association between BLLs and incident ESRD. These studies provide further evidence that links baseline blood Pb data to the development of long-term kidney disease.

In addition to the epidemiologic evidence, the expanded literature base of animal toxicological studies provide strong support that the associations reported in epidemiologic studies are the result of exposure to Pb, not reverse causality. This is due to the large amount of evidence from animal toxicological studies demonstrating health effects such as impaired kidney function and kidney damage providing additional support that associations reported in epidemiologic studies are indeed the result of exposure to Pb.

Overall, recent evidence further supports that reverse causality does not contribute substantially to the association between higher BLLs and decreases in kidney function. Several recent studies longitudinally evaluated either the change in eGFR from baseline or the development of CKD or ESRD and baseline blood Pb measurements taken years prior to the assessment of kidney function. While reverse causality may contribute to some associations between biomarkers of Pb exposure and renal function, recent evidence does not support reverse causality as the driving force behind these associations.

### 5.8.1 Summary of Reverse Causality

Epidemiologic evidence has generally reported increased associations between biomarkers of Pb exposure and renal effects, without evidence of reverse causality. Specifically, longitudinal studies evaluating a decline in eGFR in relation to blood Pb further suggest that reverse causality does not substantially affect the association between biomarkers of Pb exposure and decreased kidney function. The 2006 Pb AQCD (U.S. EPA, 2006b) reported an association between baseline BLLs and accelerated decreases in eGFR in CKD patients (Yu et al., 2004). Several recent longitudinal studies among healthy populations, free of kidney disease, also further support changes in eGFR from baseline, associated with baseline blood Pb (Chung et al., 2020; Liu et al., 2020; Harari et al., 2018; Pollack et al., 2015). Specifically, Harari et al. (2018), which had an extensive follow-up period (~16 years of follow-up), noted that increased baseline BLLs were associated with substantial decreases in eGFR from baseline.

In addition, several recent epidemiologic studies also evaluated the association between biomarkers of Pb exposure and the development of CKD or ESRD. In the population-based cohort in Sweden that also noted Pb-related reductions in eGFR, Harari et al. (2018) observed a relationship between incident CKD and BLLs at baseline, after further adjustment for baseline eGFR. Additionally, Sommar et al. (2013) combined several existing cohort studies and subsequently linked them to an ESRD database. This study identified a modest association between BLLs and incident ESRD. These studies provide further evidence that links baseline blood Pb data to the development of long-term kidney disease.

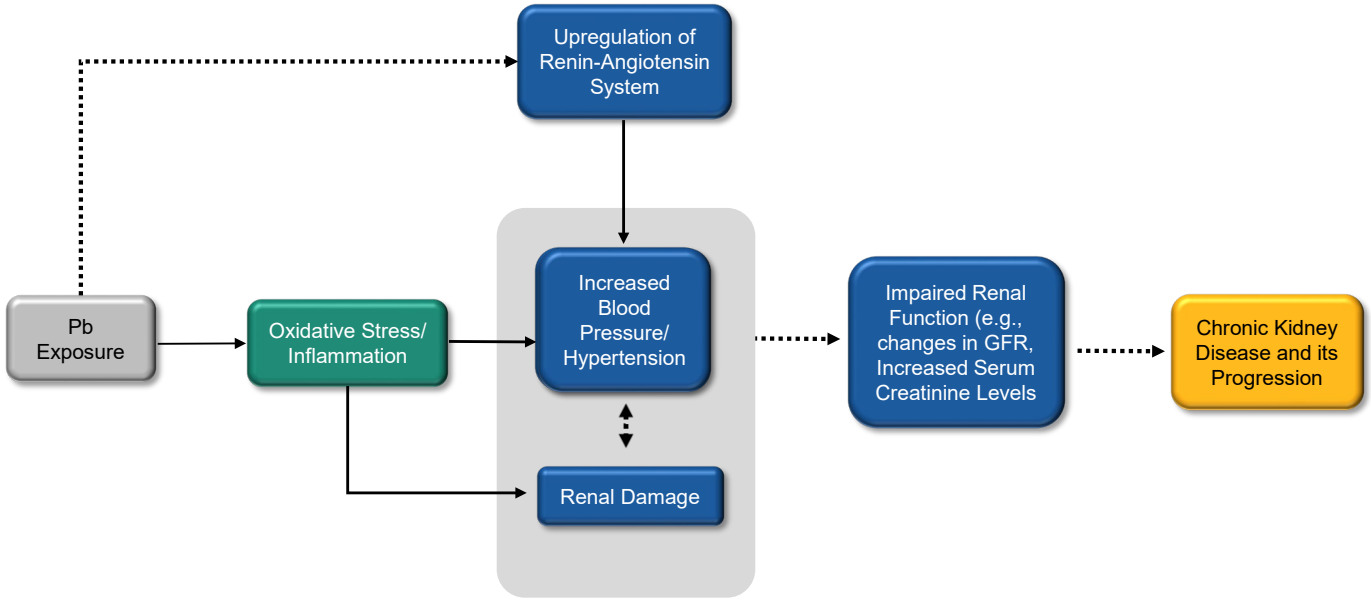
Toxicological evidence indicating associations between blood Pb and markers of oxidative stress and impaired kidney damage provides additional support that associations reported in epidemiologic studies are in fact the result of exposure to Pb. The combined toxicological and epidemiologic evidence suggests that reverse causality does not substantially contribute to the association between higher BLLs

and decreased kidney function. While reverse causality may contribute to some associations between biomarkers of Pb exposure and renal function, the available evidence does not support it as the driving force behind these associations.

## 5.9 Biological Plausibility

Sections 5.3 to 5.8 of this Appendix describe the health effects associated with exposure to Pb from epidemiologic and animal toxicological studies. Based largely on the animal toxicological evidence presented in these sections, as well as in previous ISAs and AQCDs, this section describes the biological pathways that potentially underlie the renal outcomes identified in epidemiologic studies and that are associated with Pb exposure. Figure 5-9 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical renal events associated with exposures to Pb at concentrations observed in epidemiologic studies. Note that the role of biological plausibility in contributing to the weight-of-evidence causality determinations reached in the current Pb ISA is discussed in Section 5.10.

When considering the available health evidence, plausible pathways connecting Pb exposure to the apical events reported in epidemiologic studies are presented in Figure 5-9. The first pathway begins with oxidative stress directly resulting in kidney damage and increases in blood pressure. The second pathway involves Pb activation of RAAS resulting in increases in blood pressure. Once these pathways are initiated, there is evidence from experimental and observational studies that exposure to Pb may result in a series of pathophysiological responses that could lead to adverse renal events such as CKD and kidney failure.




Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to ozone exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway or a genetic knockout model used in an experimental study involving Pb exposure Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color-coded (gray, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population level effects generally reflect the results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

**Figure 5–9 Potential biological pathways for renal effects following Pb exposure.**

It has been well established that exposure to Pb can stimulate the production of reactive oxygen species and markers of inflammation in the blood or kidneys (see (U.S. EPA, 2013)), and evidence published since the last Pb ISA further supports these findings. For example, in rats Andjelkovic et al. (2019) reported a statistically significant increase ($p < 0.05$) in total oxidative status and the oxidative stress index in blood following Pb exposure (~30 µg/dL BLL). These authors also reported a decrease ($p < 0.05$) in the total antioxidative status in blood following Pb exposure (~30 µg/dL BLL). Moreover, Pb exposure to rat primary proximal tubular cells increased intracellular reactive oxygen species production in a concentration-dependent manner (Wang et al., 2011). In both of these studies, the authors reported higher levels of lipid peroxidation (e.g., malondialdehyde or thiobarbituric acid reactive substance levels) in kidney tissue (Andjelkovic et al., 2019) and primary cells (Wang et al., 2011) relative to controls. Other studies similarly demonstrated increased indicators of lipid peroxidation in serum and renal tissue after exposure to Pb (Gao et al., 2020; Shi et al., 2020; Li et al., 2017; Laamech et al., 2016; Berrahal et al., 2011; Lodi et al., 2011; Moneim et al., 2011; Wang et al., 2011; Massó-González and Antonio-García, 2009). This is important given that lipid peroxidation can be an indicator of tissue damage and because numerous studies that included kidney histology have demonstrated abnormalities and damage to kidney cells or tissue following Pb exposure (Gao et al., 2020; Shi et al., 2020; Alcaraz-Contreras et al., 2016; Laamech et al., 2016; Basgen and Sobin, 2014; Roncal et al., 2007; Rodríguez-

Iturbe et al., 2005; Fowler et al., 1980). Some of these Pb-induced kidney changes have been found to be the result of Pb-induced cellular necrosis (Fowler et al., 1980) or apoptosis (Rana, 2008), and studies have demonstrated that inhibiting Pb-induced oxidative stress and inflammation can ameliorate kidney damage (Rana et al., 2020; Shafiekhani et al., 2019). These kidney abnormalities could plausibly result in impaired kidney function. Following exposure to Pb, markers of impaired kidney function such as increased levels of creatinine and BUN)have been reported in animal toxicological studies (Shi et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2016; Zou et al., 2015; Berrahal et al., 2011; Roncal et al., 2007). In addition, the previous ISA included studies in which exposure to Pb resulted in either decreased (Shi et al., 2020) or elevated glomerular filtration rates (GFR) (Khalil-Manesh et al., 1993; Khalil-Manesh et al., 1992b; Khalil-Manesh et al., 1992a), both of which can be indicative of kidney disease. These studies demonstrated that decreased GFR can be indicative of reduced blood filtration by the kidneys, while increased GFR can be consistent with the hyperfiltration and renal hypertrophy that can occur in advanced diabetes.

Pb-induced oxidative stress can also lead to the adverse kidney outcomes reported in epidemiologic studies through hypertension. As detailed in the cardiovascular disease appendix, oxidative stress can lead to increases in blood pressure through a number of different pathways. An increase in blood pressure due to Pb-induced oxidative stress is supported by a study demonstrating that in rats, the antioxidant vitamin E could attenuate both Pb-induced oxidative stress and blood pressure increases (Vaziri et al., 1999). This is important given that a chronic increase in blood pressure can lead to glomerular and renal vasculature injury, which could plausibly result in renal dysfunction and CKD.

The second pathway by which exposure to Pb could potentially lead to the outcomes reported in epidemiologic studies is through RAAS. RAAS plays an important role in the regulation of blood pressure and kidney homeostasis. For example, Ang II is an important part of RAAS that stimulates arteriolar vasoconstriction, leading to increases in blood pressure and hypertension, which as noted above, could plausibly contribute to kidney dysfunction, CKD, and kidney failure. Following Pb exposure, vascular reactivity to Ang II was found to increase (Robles et al., 2007). Exposure to Pb also resulted in increases in kidney and serum ACE activity as well as renal Ang II-positive cells (Rodríguez-Iturbe et al., 2005; Sharifi et al., 2004; Carmignani et al., 1999). Moreover, use of an ACE inhibitor or blocking the AT-1 receptor (which binds ANG II) ameliorated Pb-induced increases in blood pressure (Simões et al., 2011).

When considering the available evidence, there are plausible pathways connecting Pb exposure to renal effects (Figure 5-9). The first potential pathway begins with Pb-induced oxidative stress, which results in kidney damage and increases in blood pressure, while the second potential pathway is through the activation of RAAS, which can also result in an increase in blood pressure. Increased blood pressure can then lead to kidney damage and impaired function, which if sufficiently severe, can lead to kidney disease. Collectively, these proposed pathways provide biological plausibility for the associations between Pb levels and adverse renal effects reported in epidemiologic studies.

## 5.10 Summary and Causality Determination

In the 2013 Pb ISA, a suggestive relationship between exposure to Pb and renal effects was judged appropriate on the basis of the health evidence and its associated uncertainties. Studies published since the 2013 ISA greatly expand the evidence base and serve to strengthen the evidence for a relationship between exposure to Pb and renal-related health effects. In addition, more recent evidence has greatly reduced (but not eliminated) key uncertainties from the last review, particularly those associated with the potential for reverse causality in epidemiologic studies (see below). This section presents the causality determination for Pb exposures and renal effects, relying upon the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015). Key health evidence supporting this determination is also summarized in Table 5-1.

In the 2013 Pb ISA, prospective epidemiologic studies in older adult, mostly white, men supported the relationship between long-term Pb exposure and reduced kidney function at mean BLLs ≤ 10 μg/dL (Tsaih et al., 2004; Kim et al., 1996). Other population-based prospective cohort studies reported a longitudinal association between BLLs and increases in serum creatinine and CKD progression over time (Yu et al., 2004). In addition, most epidemiologic cross-sectional studies discussed in the last review reported that higher tissue Pb concentrations (e.g., blood or bone Pb levels) are associated with impaired renal function (Navas-Acien et al., 2009; Muntner et al., 2005; Muntner et al., 2003). Important uncertainties were raised in the last review with respect to the epidemiologic evidence, particularly the potential for reverse causality. That is, given the kidney's role in removing toxins from the blood, increased BLLs could result from reduced excretion due to pre-existing kidney damage rather than as the causative factor for kidney impairment. It was further noted in the last review that the existence of an association in adults with normal renal function does not preclude the possibility of reverse causation because the variation in Pb clearance within the range of normal kidney function is unknown. Other uncertainties identified in the epidemiologic evidence from the last review were related to the Pb exposure level, timing, frequency, and duration contributing to the associations reported in these studies given that most were performed in adult populations with likely higher past Pb exposures. With respect to the animal toxicology evidence, the 2013 Pb ISA noted that at BLLs >30 μg/dL, there was clear evidence that Pb exposure caused changes to the kidney morphology and function (Khalil-Manesh et al., 1992b; Khalil-Manesh et al., 1992a). Evidence for functional changes in animals at lower BLLs was more limited and therefore, more uncertain. When the health evidence was considered along with these uncertainties, particularly uncertainties related to the potential for reverse causality, the 2013 ISA concluded that evidence was suggestive of, but not sufficient to infer, a causal relationship between exposure to Pb and renal effects.

More recent epidemiologic and animal toxicological studies greatly expand the evidence base from the 2013 Pb ISA. Not only do these newer studies strengthen the evidence of a relationship between exposure to Pb and renal effects, they also serve to appreciably reduce the uncertainties identified in the last review. As noted above, the potential for reverse causality was the most influential uncertainty for the

conclusion in the last review that the scientific evidence was suggestive of, but not sufficient to infer, a causal relationship between exposure to Pb and renal effects. That is, increased BLLs could result from reduced excretion due to kidney damage (unrelated to Pb exposure) rather than as a causative factor for kidney impairment. Cross-sectional studies and studies conducted in populations that are already experiencing renal dysfunction have the greatest potential for reverse causality. However, prospective analyses that include both baseline measurements of biomarkers of Pb exposure as well as incident changes in renal function provide some assurances that associations observed across the epidemiologic literature are due to a true association with Pb and are not the result of reverse causality. Thus, it is important to note the more recent longitudinal analyses finding positive associations between exposure to Pb and kidney disease (Harari et al., 2018) and decreases in eGFR (Chung et al., 2020; Liu et al., 2020). These longitudinal studies are in agreement with other types of epidemiologic studies reporting similar associations between exposure to Pb and kidney disease (Wan et al., 2021; Hagedoorn et al., 2020; Lee et al., 2020; Wu et al., 2019; Huang et al., 2013; Sommar et al., 2013) and decreases in eGFR (Chung et al., 2020; Liu et al., 2020; Pollack et al., 2015). Additional evidence suggesting the that results in epidemiologic studies are not attributable to reverse causality comes from an epidemiologic study demonstrating that exposure to Pb is associated with changes in creatinine levels consistent with reduced kidney function and disease (Pollack et al., 2015). Importantly, this more recent creatinine study is also consistent with two longitudinal studies from the prior review presenting similar results (Tsaih et al., 2004; Kim et al., 1996). Moreover, these epidemiologic studies were performed in a number of different geographical areas and in diverse study populations, further reducing the chance that epidemiologic results are due to reverse causality.

Strong support that the associations reported in epidemiologic studies are not from reverse causality also come from the expanded literature base of animal toxicological studies. In particular, there is a large body of animal toxicological studies published since the last review largely demonstrating renal damage or structural abnormalities in rodents following exposure to Pb (Dumková et al., 2020a; Gao et al., 2020; Shi et al., 2020; Dumková et al., 2017; Alcaraz-Contreras et al., 2016; Laamech et al., 2016; Basgen and Sobin, 2014; Rodríguez-Iturbe et al., 2005; Fowler et al., 1980). With respect to concentrations, effects in rodents were observed in studies at BLLs ranging from ~3.0 µg/dL to ~30 µg/dL. It is important to note that there is some uncertainty of an effect at this lowest level given that the same study did not report similar morphological effects at higher BLLs (Basgen and Sobin, 2014) and that Carlson et al. (2018) reported that renal lesions in mice with a BLL of ~3.0 µg/dL were similar to the lesions in controls. Nonetheless, there is substantial evidence from animal histological studies for kidney abnormalities following exposure to Pb, thus providing additional support that the positive associations for renal disease and impaired renal function reported in longitudinal and cross-sectional epidemiologic studies are not due to reverse causality. Moreover, these animal toxicology studies also serve to reduce, but not eliminate, the uncertainty noted in the last review with respect to effects in animals at the lowest BLLs.

Epidemiologic studies are also coherent with animal toxicological studies in that they both provide some evidence of a positive relationship between exposure to Pb and molecular markers of impaired kidney function in blood, urine, or tissue. As noted above, the 2013 ISA (U.S. EPA, 2013) evaluated a couple of longitudinal epidemiologic studies that reported positive associations between increases in serum creatinine levels and bone Pb measurements (Tsaih et al., 2004; Kim et al., 1996). These studies are in agreement with a more recent epidemiologic study describing a positive association between increasing BLLs and serum creatinine increases in premenopausal women (Pollack et al., 2015). In coherence with these epidemiologic studies are a number of animal toxicological studies from the previous and current review with BLLs below 30 µg/dL. Although not all studies demonstrated an increase, most of these studies reported higher blood creatinine levels in Pb-exposed animals compared with controls (Shi et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2016; Zou et al., 2015; Berrahal et al., 2011; Roncal et al., 2007).

Similar to creatinine levels, changes in measures of blood urea can also be indicative of renal disease. Although there were no epidemiologic studies examining measures of urea, animal toxicological studies published since the 2013 Pb ISA (blood Pb values of ≤ 30 µg/dL) generally indicated that exposure to Pb can increase serum or kidney measures of urea (Gao et al., 2020; Shi et al., 2020; Laamech et al., 2016; Zou et al., 2015). It should be noted, however, that there is at least some variability with respect to the direction of serum urea levels following Pb exposure. In contrast to the studies mentioned above, both Andjelkovic et al. (2019) and Dumková et al. (2020a) reported a statistically significant ($p < 0.05$) decrease in measures of urea relative to controls, while other studies reported no effect (Carlson et al., 2018; Corsetti et al., 2017) (BLL of 2.89 µg/dL). It is difficult to interpret whether there is biological significance to a decrease in serum urea levels relative to control animals, but nonetheless, most animal toxicological studies reported changes in the levels of urea following exposure to Pb, with most of those changes being increases. Moreover, the results of these creatinine and urea studies further strengthen the thesis that the effects observed in epidemiologic studies are truly due to Pb exposure. Other potential markers of kidney function evaluated in epidemiologic and animal toxicological studies (e.g., UA, proteinuria) were more limited in number with varying results, and therefore, more uncertain.

As described throughout this causal determination section, there is considerable animal toxicological evidence supporting Pb as the causative agent for the positive epidemiologic associations between measures of Pb exposure and adverse health outcomes. Section 5.9 of this document includes that information to construct a plausible pathway by which exposure to Pb could result in impaired kidney function or renal disease. In brief, Section 5.10 notes that exposure to Pb can stimulate the production of reactive oxygen species in the blood or kidneys of exposed laboratory animals (see (U.S. EPA, 2013) Section 4.5.3.1). Some studies have also reported increases in lipid peroxidation in kidney tissue or primary cells relative to control animals (Section 5.9). Lipid peroxidation is often an indicator of tissue damage and thus, is consistent with the animal histology studies mentioned above demonstrating renal damage following Pb exposure. Given these results in animal toxicological studies, it is plausible that

associations with renal dysfunction and renal disease (e.g., CKD) reported in epidemiologic studies could be due to underlying kidney damage from Pb-induced oxidative stress.

The biological plausibility section (Section 5.9) also notes that Pb could potentially lead to the outcomes reported in epidemiologic studies through RAAS, which has an important role in the regulation of blood pressure and kidney homeostasis. Ang II is a component of RAAS that stimulates arteriolar vasoconstriction, leading to increases in blood pressure and hypertension, and Ang II levels can be increased by exposure to Pb (Sections 5.6 and 5.9). Importantly, prolonged blood pressure increases can eventually lead to glomerular and renal vasculature injury, plausibly resulting in the renal dysfunction and renal disease associations observed in epidemiologic studies.

In summary, the recent evidence described throughout this section extends the consistency and coherence of the evidence base reported in the 2013 Pb ISA. Recent epidemiologic and animal toxicology studies have also served to greatly reduce uncertainties noted in the previous review, especially with respect to the potential for reverse causality in epidemiologic studies. Direct evidence for Pb exposure-related renal effects can be found in numerous animal toxicological studies. In coherence with these results are epidemiologic studies which found that Pb exposure is associated with some of the same renal endpoints reported in animal toxicological studies (e.g., eGFR, blood markers of renal impairment). For some markers of renal function, there is a limited number of studies evaluating these endpoints, and there are some inconsistencies in results across some of the animal toxicological and epidemiological studies. In general, these studies largely demonstrate a relationship between exposure to Pb and indicators of kidney distress. Moreover, animal toxicological studies demonstrating renal damage following Pb exposure provide coherence and biological plausibility for the consistent epidemiologic associations reported between body Pb concentrations and renal disease. **Thus, the collective evidence is sufficient to conclude that there is a *causal relationship* between Pb exposure and renal effects.** The key evidence, as it relates to the causal framework, is summarized in Table 5-1.

## Table 5–1 Summary of evidence indicating a causal relationship between Pb exposure and renal effects.

| Rationale for Causality Determination[a] | Key Evidence[b] | References[b] | Pb Biomarker Levels Associated with Effects[c] |
|---|---|---|---|
| Generally consistent evidence from epidemiologic studies of CKD | Positive associations between body Pb measurements (e.g., blood Pb) and CKD or ESRD incidence | (Wu et al., 2019; Harari et al., 2018; Sommar et al., 2013) | BLLs: ~2 to >25 |
| Generally consistent evidence from epidemiologic studies of diabetic nephropathy | Mostly positive associations between body Pb measurements (e.g., blood Pb) and diabetic nephropathy | (Wan et al., 2021; Hagedoorn et al., 2020; Huang et al., 2013), | BLB: <80 to 600 µg<br>BLLs: ~1.5 to 6 µg/dL |
| Generally consistent evidence from epidemiologic studies of eGFR | Mostly positive associations between body Pb measurements (e.g., blood Pb) and eGFR | (Chung et al., 2020; Liu et al., 2020; Jain, 2019; Buser et al., 2016; Chung et al., 2014; Kim and Lee, 2012; Navas-Acien et al., 2009; Åkesson et al., 2005; Tsaih et al., 2004; Kim et al., 1996) | BLLs: ~3 to >30 µg/dL |
| Generally consistent evidence from epidemiologic studies for creatinine in blood or urine | Mostly positive associations between body Pb levels and increases in creatinine | (Pollack et al., 2015; Tsaih et al., 2004; Kim et al., 1996) | BLLs: ~0.9 to 10 µg/dL |
| Mostly null findings from epidemiologic studies for measures of UA | Increase in SUA among women, but not men | (Park and Kim, 2021) | BLL: ~2 µg/dL |
| | Null results between body Pb and measures of UA and hyperuricemia | (Arrebola et al., 2019; Jung et al., 2019) | BLLs: ~0.1 to 2 µg/dL |
| Generally consistent evidence from animal toxicological studies for changes in GFR | Pb-exposed rats had a statistically significantly lower ($p < 0.05$) GFR relative to control rats | (Shi et al., 2020) | BLL:~10.21 µg/dL |
| | Pb-exposed rats had a statistically significant increase in GFR indicative of renal hyperfiltration and hypertrophy | {Khalil-Manesh, 1993, 50791;Khalil-Manesh, 1992, 49502;Khalil-Manesh; 1992, 49543) | BLL: ~30–45 µg/dL |

| Rationale for Causality Determination[a] | Key Evidence[b] | References[b] | Pb Biomarker Levels Associated with Effects[c] |
|---|---|---|---|
| Consistent evidence from animal toxicological studies of kidney histology | Animal toxicological studies consistently demonstrate renal damage or abnormalities in animals following Pb exposure | (Gao et al., 2020; Shi et al., 2020; Dumková et al., 2017; Alcaraz-Contreras et al., 2016; Laamech et al., 2016; Basgen and Sobin, 2014; Rodríguez-Iturbe et al., 2005; Fowler et al., 1980) | BLL:~10–30 µg/dL |
| Some evidence from animal toxicological studies for increased creatinine in blood or urine | Most animal studies involving exposure via drinking water or gavage demonstrated a statistically significant increase in serum creatinine (or decrease in urine) following exposure to Pb | (Shi et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2016; Zou et al., 2015) | BLL:~10–30 µg/dL |
| | A single animal toxicology study using an inhalation exposure methodology reported a decrease in creatinine levels | (Dumková et al., 2020a) | BLL: ~14 µg/dL |
| | A couple of animal toxicology studies using a drinking water exposure methodology reported no change in creatinine levels in mice | (Carlson et al., 2018)<br>{Corsetti, 2017, 4856550 | BLL 2.89 µg/dL<br>BLL 21.6 µg/dL |
| Some evidence from animal toxicological studies for changes in blood or urine levels of urea | Most animal studies involving exposure via drinking water or gavage demonstrated a statistically significant increase in measures of urea following exposure to Pb | Gao, 2020, 7087494; Zou, 2015, 2830614; Shi, 2020, 7084022; Laamech, 2016, 6716234} | BLL:~10–30 µg/dL |
| | A couple of animal toxicology studies reported a decrease in urea levels | (Andjelkovic et al., 2019)<br>(Dumková et al., 2020a) | BLL:~23 µg/dL<br>BLL:~14 µg/dL |
| | An animal toxicology study reported no change in BUN levels in mice | (Carlson et al., 2018) | BLL 2.89 µg/dL |

BLB = body Pb burden; BLL = blood Pb level; BUN = blood urea nitrogen; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; Pb = lead; SUA = serum uric acid; UA = uric acid.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the Pb biomarker levels at which the evidence is substantiated.

1

## 5.11 Evidence Inventories – Data Tables to Summarize Study Details

### Table 5–2 Epidemiologic studies of Pb exposure and kidney disease.

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Harari et al. (2018)<br><br>Malmö, Sweden<br><br>Baseline: 1991–1994, Follow-up: 2007–2012<br><br>Cohort | Cardiovascular cohort of Malmö Diet and Cancer Study (MDCS-CC)<br>n = 4,341 enrolled in cohort, 2,567 followed up | Blood Pb (ICP-MS) µg/dL<br>Median: 2.5 (Range; 0.15–25.8)<br>Max: 25.8<br>Quartiles<br>Median (range)<br>Q1 1.5 (0.15–1.85)<br>Q2 2.2 (1.85–2.47)<br>Q3 2.9 (24.7–3.30)<br>Q4 4.6 (3.3–25.8)<br>Q1 + Q2 + Q3 2.2 (0.15–3.30)<br><br>Age at measurement 57 | CKD<br><br>Age of outcome 73 | Linear regression or Cox proportional hazards regression adjusted for age, sex, smoking, alcohol intake, hypertension, diabetes, waist circumference, eGFR at baseline, education level | CKD (HR)[a]<br>Q1 Reference<br>Q2 0.83 (0.54, 1.28)<br>Q3 0.83 (0.53, 1.29)<br>Q4 1.3 (0.85, 2.00)<br>Q4 vs. Q1 + Q2 + Q3<br>1.49 (1.07, 2.08) |
| Wu et al. (2019)<br><br>Taiwan<br><br>Case-control | n = 658<br><br>220 CKD patients, 438 controls (age and gender matched) | Red blood cell Pb (ICP-MS) (µg/dL)<br><br>Tertiles<br>T1 ≤ 2.794<br>T2 2.794–4.635<br>T3 > 4.635<br><br>Age at measurement<br>Mean (SE)<br>Cases 65.14 (0.91)<br>Controls 64.21 (0.60) | CKD<br><br>CKD: eGFR <60 mL/min/1.73 $m^2$ for 3 consecutive mo | Unconditional logistic regression adjusted for age, sex, educational level, alcohol, tea, and coffee drinking, analgesic use, diabetes, hypertension, urinary creatinine, total urinary arsenic, blood cadmium, and blood selenium | Blood Pb log-transformed<br>OR[a]<br>T1 Reference<br>T2 3.26 (1.58, 6.71)<br>T3 6.48 (3.23, 12.99) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Lee et al. (2020)<br><br>United States<br><br>1999–2016<br><br>Cross-sectional (EWAS) | NHANES<br>n = 46,748<br><br>Adults ≥18 | Blood Pb (ICP-MS)<br><br>Distribution not reported<br><br>Age at Measurement:<br>Mean (SD) 47 (19) | CKD<br><br>CKD 1: ACR > 30 mg/g or eGFR < 60 mL/min/1.73 $m^2$<br><br>CKD 2: ACR > 300 mg/g, or ACR > 30 mg/g and eGFR < 60 mL/min/1.73 $m^2$, or eGFR < 45 mL/min/1.73 $m^2$<br><br>CKD 3 ACR > 300 mg/g and eGFR < 60 mL/min/1.73 $m^2$, or ACR > 30 mg/g and eGFR < 45 mL/min/1.73 $m^2$, or eGFR < 30 mL/min/1.73 $m^2$) | logistic regression adjusted for age, sex, diabetes, hypertension, BMI, race/ethnicity, smoking, and SES | Per SD of the log-transformed blood Pb concentration<br>OR[a]<br><br>CKD 1<br>Discovery set: 1.27 (1.12, 1.45)<br>Validation set: 1.12 (1.00, 1.24)<br><br>CKD 2<br>Discovery set: 1.43 (1.29, 1.58)<br>Validation set: 1.45 (1.29, 1.63)<br><br>CKD 3<br>Discovery set: 1.73 (1.54, 1.95)<br>Validation set: 1.61 (1.35, 1.90) |
| Kim et al. (2015)<br><br>South Korea<br><br>2011<br><br>Cross-sectional | KNHANES<br>n = 1,797<br>Participants ≥20 yr of age | Blood Pb (GFAAS) (µg/dL)<br>Mean (SD) 2.37 (1.02)<br><br>Age at Measurement:<br>Mean (SD) 46 (14) | CKD<br>(eGFR < 60 mL/min/1.73 $m^2$ or ACR ≥ 30 mg/g) | logistic regression adjusted for age, sex, BMI, smoking, hyperlipidemia, hypertension, diabetes, blood mercury, and blood cadmium | OR: 1.05 (0.85, 1.30)[a,b] |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Sommar et al. (2013)<br><br>Sweden<br><br>1985 for Västerbotten Intervention Project, 1985 for MONICA, 1995 for Mammography Screening Project, and 1991–1996 for Malmö Diet and Cancer study. Follow-up through linkage to Swedish Renal Registry in 2006<br><br>Prospective nested case-referent (mean 7.7 yr of follow-up, range 1–16 yr) | Västerbotten Intervention Project, the Northern Sweden WHO Monitoring of Trends and Cardiovascular Disease (MONICA) study, Mammography Screening Project, and Malmö Diet and Cancer study<br>n = 118 cases and 378 controls | Blood (erythrocyte Pb measured by ICP-MS) (µg/dL)<br>Geometric Mean<br>Cases 6.62<br>Referents 5.50<br><br>Age at Measurement: Mean (Range) 63 (40–80) | ESRD (GFR < 10–15 mL/min), starting renal replacement therapy (i.e., dialysis or transplantation) | Conditional logistic regression adjusted for diabetes, BMI, and hypertension<br><br>Three controls (referents) matched to each ESRD cases by cohort, age, sex, and time of sampling | OR<br>1.14 (1.03, 1.26) |
| Huang et al. (2013)<br><br>China<br>24-mo observation period<br><br>Cohort | n = 85<br><br>Patients with type 2 diabetes with nephropathy (aged 30–83) | BLB (X-ray fluorescence and EDTA) (µg)<br>Low (BLB < 80 µg)<br>Mean (SD) 58.1 (16.7)<br>Max: 79.8<br>High (BLB 80–600 µg)<br>Mean (SD) 132.4 (46.1)<br>Max 316.8<br>Blood (ETAAS) (µg/dL)<br>Low (BLB < 80 µg)<br>Mean (SD) 3.8 (3.0)<br>Max 10.4<br>High (BLB 80–600 µg)<br>Mean (SD) 4.6 (3.1)<br>Max: 10.3<br><br>Age at Measurement<br>Mean (SD) 60.1 (9.5) Range 33–83 | Diabetic Nephropathy<br><br>eGFR<br><br>Primary outcome (2-fold increase in serum creatinine from baseline values, need for long-term dialysis, or death) | Longitudinal multivariate analysis or Cox regression analysis adjusting for age, sex, smoking, BMI, history of CVD, MAP, cholesterol, triglycerides, HbA1c, serum creatinine, daily protein intake, daily protein excretion | eGFR (mL/min/1.73 $m^2$)[c]<br>1 µg increase in BLB<br>−0.022 (−0.039, −0.005)<br>1 µg/dL increase in Blood Pb<br>−0.298 (−0.525, -0.071)<br><br>Primary outcome<br>BLB: HR: 1.01 (95% CI: 1.01, 1.02)<br>BLB > 80 µg: HR 2.79 (CI: 1.25, 6.25) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Hagedoorn et al. (2020)<br><br>The Netherlands<br><br>2009–2016<br><br>Cross-sectional | DIAbetes and LifEstyle Cohort Twente-1 (DIALECT-1)<br>n = 231<br><br>With type 2 diabetes | Blood Pb (ICP-MS) (µg/dL)<br><br>Median (IQR) 1.45 (0.83, 1.86)<br><br>Age at Measurement: Mean (SD) 64 (9) | DKD<br>(Creatinine clearance < 60 mL/min/1.73 $m^2$) and/or presence of albuminuria (ALB excretion > 30 mg/d) | Logistic regression adjusted for age, sex, HbA1c, insulin use, yr of diabetes, MAP, alcohol intake, pack yr, and blood cadmium | OR for doubling of blood Pb (log 2 transformed) (µmol/L)[a]<br><br>Creatinine clearance < 60 mL/min/1.73 $m^2$<br>OR 1.83 (1.07, 3.15)<br><br>Albuminuria > 30 mg/d<br>OR 1.75 (1.11, 2.74) |
| Wan et al. (2021)<br><br>China<br><br>May–August 2018<br><br>Cross-sectional | Environmental Pollutant Exposure and Metabolic Diseases in Shanghai n = 4,234 | Blood (AAS) Pb (µg/dL) Median (IQR)<br>2.6 (1.8, 3.6)<br><br>Age at Measurement Median (IQR)<br>67 (62–72) yr | DKD<br><br>ACR (high, ≥30 mg/g); DKD as defined by American Diabetes Association (ACR > 30 mg/g or eGFR < 60 mL/min per 1.73 $m^2$) | Linear or logistic regression adjusting for age, sex, duration of diabetes, education status, current smoking, BMI, HbA1c, dyslipidemia, hypertension | OR (4th vs. 1st quartile of Blood Pb)[a]<br><br>DKD 1.36 (1.06, 1.74)<br><br>ACR (>30 mg/g) 1.31, (1.02, 1.69)) |
| Hara et al. (2016)<br><br>Northeastern Belgium Baseline blood Pb (1985–1989), follow-up through 2014<br><br>Cohort | Cadmium in Belgium (CadmiBel) study<br>n = 1,302<br><br>Flemish residents (>20 yr), randomly recruited from 10 districts in northeastern Belgium | Blood Pb (ETAAS with Zeeman correction) (µg/dL)<br>Geometric Mean (IQR) 6.00 (3.31, 10.35)<br><br>Age at Measurement: Mean (SD) 47.8 (15.6) | Nephrolithiasis (Self-reported and verified by investigators against medical records. Cases were symptomatic, and often hospitalized for diagnosis and treatment) | Cox regression adjusted for age, sex, serum magnesium, 24 hr urinary volume, and calcium | Per doubling of blood Pb (µmol/L)[a] (HR)<br><br>Baseline Pb 1.35 (1.06, 1.73)<br>Mean (baseline and follow-up averaged): 1.32 (1.03, 1.71)<br>Baseline with regression dilution bias correction 1.44 (1.07, 1.93) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Sun et al. (2019)<br><br>2007–2016<br><br>Cross-sectional | NHANES<br>n = 21,402<br><br>Adult (>20 yr) participants from NHANES | Blood Pb (ICP-MS)[d] (µg/dL)<br>Median: 1.22<br>95th: 3.89<br>Max: 61.29 | Nephrolithiasis (Self-reported history of kidney stones) | Logistic regression adjusting for age, sex, race/ethnicity, BMI, educational level, marital status, annual family income, smoking, physical activity, intake of total energy, calcium, phosphate, sodium, potassium, magnesium, total fluid, alcohol, caffeine, vitamin B6, vitamin C, and vitamin D, and eGFR | Weighted OR (95% CI)<br><br>Compared with reference level (0.05 µg/dL)<br>0.50 µg/dL: 0.88 (0.81, 0.95)<br>1.00 µg/dL: 0.75 (0.63, 0.89)<br>1.50 µg/dL: 0.67 (0.52, 0.85)<br>2.00 µg/dL: 0.62 (0.46, 0.83)<br>2.5 µg/dL: 0.60 (0.44, 0.82)<br>3.0 µg/dL: 0.60 (0.43, 0.84)<br>3.5 µg/dL: 0.60 (0.44, 0.86)<br>4.0 µg/dL: 0.61 (0.44, 0.86)<br>4.5 µg/dL: 0.63 (0.45, 0.88)<br>5.0 µg/dL: 0.64 (0.46, 0.90) |

AAS = angiotensin-aldosterone system; ACR = albumin-to-creatinine ratio; ALB = albumin; BLB = body Pb burden; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; EDTA = ethylenediaminetetraacetic acid; ESRD = end stage renal disease; ETAAS = Electrothermal Atomic Absorption Spectrometry; EWAS = environment wide association study; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HR = hazard ratio; hr = hour; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; IQR = interquartile ratio; MAP = mean arterial pressure; MDCS-CC = cardiovascular cohort of the Malmö Diet and Cancer Study; mo = months; MONICA = Monitory of Trends and Cardiovascular Disease; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; Q = quartile; SE = standard error; SES = socioeconomic status; T = tertile; yr = year.

*Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th-90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[a]Unable to be standardized.

[b]Increment unclear.

[c]Confidence intervals estimated based on reported p-values.

[d]Blood Pb analysis method not reported, assumed based on data set (NHANES).

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## Table 5–3 Animal toxicological studies of Pb exposure and kidney histology.

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Basgen and Sobin (2014) | Mouse<br>Control<br>(Pb-free drinking water), M/F, n = 12, (6/6)<br><br>30 ppm, M/F, n = 12, (6/6)<br><br>330 ppm, M/F, n = 12, (6/6) | In utero to PND 28 | Drinking water from dams was treated with 99.4% Pb acetate. Litters were then exposed to 0, 30, or 330 Pb acetate in drinking water for 28 d | 0.03 ± 0.01 µg/dL for control males<br><br>0.03 ± 0.01 µg/dL for control females<br><br>3.63 µg/dL ± 0.71 µg/dL for 30 ppm males<br><br>2.74 µg/dL ± 0.36 µg/dL for 30 ppm females<br><br>16.02 µg/dL ± 3.25 µg/dL for 330 ppm males<br><br>13.35 µg/dL ± 1.31 µg/dL for 330 ppm females | Kidney Histology, podocyte characteristics and glomerular volume post 4-wk exposure |
| Li et al. (2017) | Mouse (Balb/c)<br>Control<br>(water), F, n = 8<br><br>100 mg/kg/d Pb acetate, F, n = 8 | 6–7 wk old mice 8 wk | Plain water or 100 mg/kg/d Pb acetate for 1 d then given skim milk from d −2–15 | 0.43 ± 0.05 µg/L for control (4.3 ± 0.05 µg/dL)<br><br>302.20 ± 25.32 µg/L for 100 mg/kg/d Pb acetate (30.2 ± 25.32 µg/dL) | Kidney Histology post exposure |
| Alcaraz-Contreras et al. (2016) | Rat (Wistar)<br>Control (water), M, n = 5<br><br>2,000 ppm Pb acetate, M, n = 5 | 2 mo old rats exposed to Pb for 8 wk | 2 mo old rats received drinking water, or drinking water with 2000 ppm Pb acetate for 8 wk | 21.9 ± 2.0 µg/dL for 2000 ppm group | Kidney Histology1 d post 8-wk exposure |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Rahman et al. (2018) | Rat (Wistar)<br>Control (tap water), M/F, n = 7–8<br><br>0.2% Pb acetate, M/F, n = 7–8/group | PND 1 to PND 30 | Pups were exposed to 0.2% Pb acetate from PND 1 to PND 21 through dam's drinking water. Then rats were exposed directly through drinking water until PND 30. Control animals were given tap water throughout | 2.2 ± 0.7 µg/dL for control–PND 21<br><br>12.4 ± 3.3 µg/dL for 0.2% Pb acetate–PND 21<br><br>3.3 ± 1.7 µg/dL for control–PND 30<br><br>22.7 ± 6.0 µg/dL for 0.2% Pb acetate–PND 30 | Kidney Histology at PND 21 and PND 30 |
| Andjelkovic et al. (2019) | Rat (Wistar)<br>Control water, M, n = 8<br><br>150 mg/kg b.w., M, n = 6 | Single exposure by oral gavage (age of rats not reported) | Single oral dose of 150 mg/kg b.w. Pb acetate | ~25 µg/L for control (~2.5 µg/dL)<br><br>~225 µg/L for 150 mg/kg b.w. Pb acetate (~22.5 µg/dL) | Kidney histology 24-hr post exposure |
| Carlson et al. (2018) | Mouse (Control) (water), M/F, n = 16<br><br>0.03 mM Pb, M/F, n = 8 | Treatment began no earlier than an age of 5 wk for 11 wk | Pb-free water or 0.03 mM Pb acetate dissolved in drinking water for 11 wk | Control (water) not detected<br><br>2.89 ± 0.44 µg/dL for 0.03 mM | Kidney Histology one wk after 11 wk exposure |
| Dumková et al. (2017) | Mouse<br><br>Experiment 1:<br>Control (clean air), F, n = 5 | Adult mice exposed for 6 wk | Experiment 1:<br>1.23 × $10^6$ particles/$cm^3$ of PbO inhalation exposure or clean air for 6 wk (24/hr d, 7 d a wk)<br><br>Experiment 2: | <11 ng/g for control (<1.166 µg/dL)<br><br>132 ng/g for Pb-exposed (13.992 µg/dL; not specified from which experiment measurement was derived) | Kidney Histology post 6 wk exposure |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| | 1.23 × $10^6$ PbO particles/$cm^3$, F, n = 5<br><br>Experiment 2:<br>Control (clean air), F, n = 5<br><br>0.956 × $10^6$ particles/$cm^3$, F, n = 5 | | 0.956 × $10^6$ particles/$cm^3$ of PbO inhalation exposure or clean air for 6 wk (24/hr d, 7 d a wk)<br><br>(Experiment 2 was a replicant of experiment 1): | | |
| Laamech et al. (2016) | Mouse<br>Control (distilled water), M/F, n = 10<br><br>5 mg/kg/d Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | Distilled water or 5 mg/kg/d Pb acetate dissolved in distilled water for 40 d | 0.009 µg/mL for control (distilled water) (0.9 µg/dL)<br><br>0.18 µg/mL for 5 mg/kg/d Pb acetate (18 µg/dL) | Kidney Histology 2 d post exposure |
| Shi et al. (2020) | Rat (SD)<br>Control (deionized water), M, n = 8<br><br>0.5% Pb acetate, M, n = 8 | 28 d after PND 21 | After 21 d of milk feeding, 0.5% Pb acetate or deionized water for 28 d | 0.18 ± 0.07 µg/dL for Control (deionized water)<br><br>10.21 ± 0.93 µg/dL for 0.5% Pb acetate | Kidney Histology post exposure |
| Gao et al. (2020) | Rat (SD)<br>Control (Distilled water), M/F, n = 10<br><br>5 mg/kg Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | 5 mg/kg Pb acetate orally for 35 d followed by recovery to d 63 | <0.02 mg/kg for distilled water (<2.12 µg/dL)<br><br>0.10 ± 0.03 mg/kg for 5 mg/kg Pb acetate (d 64) (10.6 ± 0.03 µg/dL) | Kidney Histology following the end of the experiment on d 63 |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Dumková et al. (2020b) | Mouse (Control) (clean air), F, n = 10 (wk, 6 wk, 11 wk)<br><br>PbO, F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO recovery, F, n = 10 (6 wk PbO, 5 wk clean air) | Age of mice in experiment unclear | PbO 78.0 µg PbO/$m^3$ or clean air for 24 hr/d 7 d/wk for 2 wk, 6 wk, or 11 wk. A recovery group was exposed to PbO for 6 wk and then clean air for 5 wk (11 wk total) | <3 ng/g in control (2 wk, 6 wk, 11 wk) (0.3 µg/dL)<br><br>104 ng/g PbO 2 wk (10.4 µg/dL)<br><br>148 ng/g PbO 6 wk (14.8 µg/dL)<br><br>174 ng/g PbO 11 wk (17.4 µg/dL) | Kidney histology at 2 wk, 6 wk, and 11 wk |
| Dumková et al. (2020a) | Mouse (Control) (clean air), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk)<br><br>Pb(NO3)2 (68.6 µg/$m^3$), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk)<br><br>Recovery (Pb(NO3)2 68.6 µg/$m^3$), F, n = 10 (6 wk Pb/5 wk recovery) | 6–8 wk old mice exposed for 3 d, 2 wk, 6 wk, or 11 wk | $Pb(NO_3)$ (68.6 µg/m^3) or clean air-exposed mice for 3 d, 2 wk, 6 wk, or 11 wk. To assess recovery, a separate group of mice were exposed for 11 wk followed by 5 wk of clean air | <0.3 ng/g for control at all timepoints (<0.3 µg/dL) (d 3, 2 wk, 6 wk, 11 wk)<br><br>31 ng/g for $Pb(NO_3)_2$ d 3 (3.1 µg/dL)<br><br>40 ng/g for Pb(NO3)2 2 wk (4.0 µg/dL)<br><br>47 ng/g for Pb(NO3)2 6 wk (4.7 µg/dL)<br><br>8 5 ng/g for Pb(NO3)2 11 wk (8.5 µg/dL)<br><br>10 ng/g for Pb(NO3)2 exposure 6 wk and clean air for 5 wk (1.0 µg/dL) | Kidney Histology post 3 d, 2 wk, 6 wk, 11 wk, and 11 wk plus clearance for 5 wk (~16 wk) |

d = days; hr = hours; mo = months; M = male; M/F = male/female; $NO_3$ = nitrate, PND = postnatal day, $Pb(NO_3)_2$ = Pb nitrate, PbO = Pb oxide; wk = weeks.

## Table 5–4 Epidemiologic studies of Pb exposure and estimated glomerular filtration rate.

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Yu et al. (2004)<br><br>Taipei, Taiwan; 48-mo longitudinal study period<br><br>Cohort | Adult CKD patients<br>n = 121 | Blood Pb (ETAAS with Zeeman correction) (µg/dL)<br>Mean (SD)<br>4.2 (2.2)<br>10th–90th percentile<br>2.0–5.1 | Change in eGFR (MDRD) over 4 yr (mL/min/1.73 m²) | Cox proportional hazard model examined whether a predictor was associated with renal function including age, sex, BMI, hyperlipidemia, hypertension, smoking, use of ACE inhibitor, baseline serum creatinine, daily protein<br>excretion daily protein intake, underlying kidney disease | Change in eGFR per 1 µg/dL increase in blood Pb<br><br>−4.01 (−7.24, −0.78)[a] |
| Harari et al. (2018)<br><br>Malmö, Sweden<br><br>Baseline: 1991–1994, Follow-up: 2007–2012<br><br>Cohort | Cardiovascular cohort of Malmö Diet and Cancer Study (MDCS-CC)<br>n = 4,341 enrolled in cohort, 2,567 followed up | Blood Pb (ICP-MS) µg/dL<br>Median: 2.5 (Range; 0.15–25.8)<br>Max: 25.8<br><br>Quartiles<br>Median (range)<br>Q1 1.5 (0.15–1.85)<br>Q2 2.2 (1.85–2.47)<br>Q3 2.9 (24.7–3.30)<br>Q4 4.6 (3.3–25.8)<br>Q1 + Q2 + Q3 2.2 (0.15–3.30)<br><br>Age of measurement 57 | Change in eGFR (CKD-EPI) from baseline<br><br>Age of outcome 73 | Linear regression adjusted for age, sex, smoking, alcohol intake, hypertension, diabetes, waist circumference, eGFR at baseline, education level | Change in eGFR[c] (mL/min/1.73m$^2$)<br>Q1 (Reference)<br>Q2 −1.70 (−3.10, −0.26)<br>Q3 −2.90 (−4.30, −1.50)<br>Q4 −2.30 (−3.80, −0.73) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Liu et al. (2020)<br><br>Shiyan City of Hubei Province<br>China<br><br>Baseline between September–June 2010, follow-up in 2013<br>Mean follow-up: 4.6 yr<br><br>Cohort | Dongfeng-Tongji<br><br>n = 1,434<br><br>Retirees from Dongfeng Motor Corporation | Blood Pb (ICP-MS) µg/dL<br>Median (IQR)<br>1.23 (0.84–1.90)[b]<br>Quartiles<br>Q1 < 0.843<br>Q2 0.843–1.232<br>Q3 1.232–1.895<br>Q4 > 1.895<br><br>Age at Measurement: Mean (SD) 62.4 (7.5) | Annual eGFR (CKD-EPI) decline ([Baseline eGFR-eGFR at follow-up]/ number of follow-up yr) | Linear regression adjusted for age, sex, baseline eGFR, batch (from the 3 case-controls), occupational category, BMI, smoking status, drinking status, education level, and fasting plasma glucose | Annual decline in eGFR (mL/min/1.73 $m^2$) per ln-transformed increase in blood Pb[c,d]<br>Q1 Referent<br>Q2 0.30 (−0.20, 0.81)<br>Q3 0.30 (−0.20, 0.81)<br>Q4 0.83 (0.31, 1.35) |
| Chung et al. (2020)<br><br>Taiwan<br>Recruited 2010–2011 and follow-up in 2015–2016<br><br>Cohort | n = 770<br>Community residents living near an EAF | Blood Pb (ICP-MS) (µg/dL)<br>Geometric mean (IQR)<br>Distance from EAF<br>< 500 m 2.41 (1.22–6.19)<br>500–1000 m 2.26 (1.16–4.83)<br>1000–1500 m 2.12 (1.05–4.67)<br>1500–2000 m 2.23 (0.98–4.31)<br>>2000 m: 2.03 (1.03–4.31)<br><br>Age at measurement<br>Median 60 | eGFR (method not specified) | General linear models adjusting for age, sex, ethnicity, living near the main road and smoking | Per 1 µg increase in blood Pb: (mL/min/1.73 $m^2$)<br><br>eGFR: −2.25 (−3.50, −1.01) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Pollack et al. (2015)<br><br>Buffalo, NY<br>United States<br><br>2 menstrual cycles (8 visits per cycle) 2005–2007<br><br>Cohort | BioCycle<br>n = 259<br><br>Premenopausal women followed for 2 menstrual cycles | Blood Pb (ICP-MS) (µg/dL)<br>Median (IQR) 0.86 (0.68–1.2)<br>Mean (SD) 1.03 (0.63)<br><br>Age at Measurement:<br>Mean (SD) 27.4 (8.2) | eGFR (MDRD) | Linear mixed models adjusted for age, BMI, race, average calories, alcohol intake, smoking, and cycle day | Percent Change in Kidney Biomarkers per 2-fold increase in blood Pb[d]<br>eGFR: −3.73 (−6.55, −0.83)<br><br>OR<br>eGFR (<90 mL/min/1.73 $m^2$)<br>0.32 (0.08, 1.21)<br>eGFR (<60 mL/min/1.73 $m^2$)<br>0.32 (0.08, 1.21)<br><br>Results presented as percent change in nontransformed outcome per 2-fold increase in nontransformed exposure |
| Navas-Acien et al. (2009)<br><br>United States<br><br>1999–2006<br><br>Cross-sectional | NHANES<br>adults<br>n = 14,778<br>Aged ≥20 yr | Blood Pb (ICP-MS) (µg/dL)<br>Geometric mean 1.58<br><br>Quartiles<br>Range (Median)<br>Q1: ≤ 1.1 (0.8)<br>Q2: 1.2 to 1.6 (1.3)<br>Q3: 1.7 to 2.4 (1.9)<br>Q4: >2.4 (3.2)<br><br>Age of measurement<br>Mean (SD)<br>Reduced eGFR 67.6 (0.5)<br>No reduced eGFR 44.7 (0.3) | Reduced eGFR (MDRD) (eGFR < 60 mL/min/1.73 $m^2$) | Logistic regression adjusted for survey year, age, sex, race/ethnicity, BMI, education, smoking, cotinine, alcohol intake, hypertension, diabetes, menopausal status | OR<br>Q1 Referent<br>Q2 1.21 (0.64, 2.28)<br>Q3 1.32 (1.00, 1.76)<br>Q4 1.20 (1.07, 1.36) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Mujaj et al. (2019)<br><br>United States<br><br>May 2015 to September 2017<br><br>Cross-sectional | SPHERL<br>n = 447 men<br><br>Newly hired Pb workers at battery manufacturing and Pb recycling plants | Blood Pb (ICP-MS) (µg/dL)<br>Geometric mean (IQR)<br>1.66 (1.3–2.5)<br><br>Age at Measurement: Mean (SD) 28.7 (10.2) | eGFR (CKD-EPI), ACR | Linear regression adjusted for age, MAP, BMI, smoking, waist-to-hip ratio, total cholesterol to HDL ratio, plasma glucose, γ-glutamyl transferase, and antihypertensive drug treatment | Per doubling of blood Pb (mL/min/1.73 $m^2$)[d]<br>eGFRcrt (serum creatinine)<br>−0.135 (−3.40, 3.13)<br>eGFRcys (serum cystatin)<br>−0.222 (−3.07, 2.62)<br>eGFRcc (serum creatinine and cystatin): −0.281 (−3.07, 2.50)<br><br>Per doubling of blood Pb (mg/mmol)<br>ACR: −0.071 (−0.14, 0.59) |
| Kim and Lee (2012)<br><br>South Korea 2008–2010<br><br>Cross-sectional | KNHANES<br>n = 5,924<br>Participants ≥20 yr of age | Blood Pb (GFAAS with Zeeman correction) (µg/dL)<br>Geometric mean (95% CI) 2.289 (95% CI: 2.258, 2.319)<br>Quartiles<br>Q1 ≤ 1.743<br>Q2 > 1.734–2.305<br>Q3 > 2.305–3.010<br>Q4 > 3.010 | eGFR (MDRD)<br>(Considered reduced if < 80 mL/min per 1.73 $m^2$) | Linear and logistic regression adjusted for age, sex, residence area, education level, smoking status, drinking status, hypertension, diabetes, hemoglobin, blood cadmium, and blood mercury | Continuous eGFR[d] (mL/min/1.73 $m^2$)<br>Doubling of Pb<br>−2.624 (−3.803, −1.445)<br><br>Q1 Reference<br>Q2 −0.491 (−2.048, 1.0651)<br>Q3 −2.341 (−4.013, −0.669)<br>Q4 −3.835 (−5.730, −1.939)<br><br>Reduced eGFR (OR (95% CI))[d]<br>Doubling of Pb<br>1.324 (1.139, 1.540)<br>Q1 Reference<br>Q2 1.031 (0.806, 1.319)<br>Q3 1.161 (0.892, 1.511)<br>Q4 1.631 (1.246, 2.136) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Chung et al. (2014)<br><br>South Korea<br><br>2008<br><br>Cross-sectional | KNHANES<br>n = 2,005<br><br>≥20 yr with data for blood Pb and cadmium. Pregnant women were excluded | Blood Pb (GFAAS with Zeeman correction) (µg/dL)<br>Geometric mean: 2.5<br>Quartiles (Mean)<br>Q1 1.38<br>Q2 2.10<br>Q3 2.74<br>Q4 4.13<br><br>Age at Measurement: Mean (Range) 46 (20–87) | eGFR (CKD-EPI) | Linear regression adjusted for age, sex, smoking, hypertension, or diabetes. Logistic regression adjusted for age, sex, smoking hypertension, BMI, and blood cadmium | Per 1 µg/dL increase in blood Pb (mL/min/1.73 $m^2$)<br>−2.61 (95% CI: −3.29, −1.97)<br><br>OR (95% CI) (Q4 vs. Q1, per 1 µg/dL increase in blood Pb eGFR (<60 mL/min/1.73 $m^2$)<br>1.08 (95% CI: 0.99, 1.17) |
| Buser et al. (2016)<br><br>United States<br><br>2007–2012<br><br>Cross-sectional | NHANES<br>n = 4,875<br><br>Pregnant and breastfeeding women were excluded | Blood Pb (ICP-MS) (µg/dL)<br>Quartiles<br>Q1 ≤ 0.79<br>Q2 0.80–1.20<br>Q3 1.21–1.82<br>Q4 > 1.82 µg/dL<br><br>Age at Measurement<br>Geometric Mean 44.1 | eGFR (CKD-EPI) | Linear regression adjusting for age, race/ethnicity, sex, diabetes, alcohol intake, education, smoking status, body weight, hypertension, weak/failing kidney, serum cotinine, and blood cadmium | eGFR (mL/min/1.73 $m^2$)[d]<br>Q1 Reference<br>Q2 −1.17 (−2.91, 0.57)<br>Q3 −1.62 (−3.60, 0.36)<br>Q4 −2.67 (-4.78, −0.56) |
| Jain (2019)<br><br>United States<br><br>2003–2014<br><br>Cross-sectional | NHANES<br>n = 25, 427<br><br>≥20 yr of age | Blood Pb (ICP-MS) (µg/dL)<br><br>75th percentile: 2.15<br><br>Age at measurement ≥20 yr | Reduced eGFR (CKD-EPI) (<60 mL/min/1.73 $m^2$) | Logistic regression adjusting for sex, race/ethnicity, smoking status, age, BMI, survey year, fasting time, poverty income ratio, diabetes, and hypertension | OR (95% CI)[c,d]<br><br>eGFR (<60 mL/min/1.73 $m^2$): 1.567 (1.346, 1.823) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Lee et al. (2020)<br><br>United States<br><br>1999–2016<br><br>Cross-sectional | NHANES<br>n = 46,748<br><br>Adults ≥18 yr of age | Blood Pb (ICP-MS)<br>Distribution not reported<br><br>Age at Measurement:<br>Mean (SD) 47 (19) | Reduced eGFR (CKD-EPI) (<60, <45, or <30 mL/min/1.73 $m^2$) | Logistic regression adjusted for age, sex, diabetes, hypertension, BMI, race/ethnicity, smoking, and SES | Per SD of the log-transformed blood Pb concentration[d]<br>OR eGFR (<60 mL/min/1.73 $m^2$)<br>Discovery set: 1.35 (1.24, 1.48)<br>Validation set 1.27 (1.11, 1.45)<br><br>OR eGFR (<45 mL/min/1.73 $m^2$)<br>Discovery set: 1.60 (1.39, 1.85)<br>Validation set 1.63 (1.42, 1.88)<br><br>OR eGFR (<30 mL/min/1.73 $m^2$)<br>Discovery set: 1.98 (1.50, 2.62)<br>Validation set 2.25 (1.75, 2.90) |

ACE = angiotensin-converting enzyme ACR = albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = Method of eGFR calculation from the Chronic Kidney Disease Epidemiology Collaboration; EAF = electric arc furnace; eGFR = estimated glomerular filtration rate; ETAAS = Electrothermal Atomic Absorption Spectrometry; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; HDL = high-density lipoprotein; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; IQR = interquartile range; KNHANES = National Health and Nutrition Examination Survey; MAP = mean arterial pressure; MDCS-CC = cardiovascular cohort of the Malmö Diet and Cancer Study; MDRD = Method of eGFR calculation from the Modification of Diet in Kidney Disease study; mo = months; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Q = quartile; SD = standard deviation; SES = socioeconomic status; SPHERL = Study for Promotion of Health in Recycling Lead; Pb = lead; yr = years.

*Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th-90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[a]Confidence interval estimated from reported p-value.

[b]Units converted from µg/L.

[c]Increment unclear.

[d]Unable to be standardized.

## Table 5–5 Animal toxicological studies of Pb exposure and glomerular filtration rate.

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL | Endpoints Examined |
|---|---|---|---|---|---|
| Shi et al. (2020) | Rat (SD)<br>Control (deionized water), M, n = 8<br>0.5% Pb acetate, M, n = 8 | 28 d after PND 21 | After 21 d of milk feeding, 0.5% Pb acetate or deionized water for 28 d | 0.18 ± 0.07 µg/dL for Control (deionized water)<br>10.21 ± 0.93 µg/dL for 0.5% Pb acetate | GFR postexposure |

d = days; GFR = glomerular filtration rate; M = male; Pb = lead; PND = postnatal day; SD = standard deviation.

## Table 5–6 Epidemiologic studies of Pb exposure and albumin, creatinine, and albumin-to-creatinine ratio.

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Tsaih et al. (2004)<br><br>Boston, MA<br><br>1991–1995, ~4 yr of follow-up<br><br>Cohort | NAS<br>n = 448<br><br>Adult males, mostly white | Blood Pb (Blood (GFAAS with Zeeman correction) (µg/dL)<br>Mean (SD) 6.5 (4.2)<br>10th–90th 2.1–7.6<br><br>Bone Pb (K-XRF) (µg/g)<br>Mean (SD)<br>Tibia 21.5 (13.5)<br>Patella 32.4 (20.5)<br><br>Age at measurement<br>Mean (SD) 66.0 (6.6) | Change in serum creatinine (mg/dL) per yr<br><br>Age at outcome<br>Mean (SD) 72.0 (6.5) | Log linear regression adjusted for age, BMI, hypertension, diabetes, smoking status, alcohol consumption, analgesic use, baseline serum creatinine | Annual change in serum creatinine (mg/dL/yr)<br>Blood Pb<br>Overall 0.002 (−0.001, 0.004)<br>Diabetic 0.013 (0.005, 0.02)<br>Nondiabetic 0.001 (0, 0.002)<br>Hypertensive 0.001 (−0.002, 0.005)<br>Normotensive 0.002 (0, 0.003)<br><br>Tibia Pb<br>Overall, 0.035 (−0.014, 0.084)<br>Diabetic 0.412 (0.146, 0.678)<br>Nondiabetic 0.025 (−0.024, 0.074)<br>Hypertensive 0.116 (0.017, 0.214)<br>Normotensive 0.002 (−0.057, 0.061) |
| Kim et al. (1996)<br><br>Boston, MA<br><br>1979–1994<br><br>Retrospective cohort | NAS<br>n = 459<br><br>Adult males, mostly white | Blood Pb (Blood (GFAAS with Zeeman correction) (µg/dL)<br>Median 8.6<br>10th–90th percentile: 4.0–17.5 | Change in Serum creatinine (mg/dL) | Random-effects modeling adjusted for baseline age, time since initial visit, BMI, smoking status, alcohol ingestion, education level, and hypertension | Change in serum creatinine (mg/dL)<br>Peak blood Pb ≤ 40 µg/dL<br>0.0017 (0.0005, 0.003)<br>Peak blood Pb ≤ 25 µg/dL<br>0.0021 (0.0007, 0.0035)<br>Peak blood Pb ≤ 10 µg/dL<br>0.0033 (0.0012, 0.0053) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Åkesson et al. (2005)<br><br>Sweden<br><br>1999–2000<br><br>Cross-sectional | WHILA, adult women<br>n = 820 | Median (5–95% CI) concurrent blood Pb: 2.2 (1.1, 4.6) µg/dL<br>10th–90th percentile: 1.3–3.8 | Creatinine clearance/100 (mL/min) | Linear regression adjusted for age, BMI, diabetes, hypertension, regular use of nephrotoxic drug, smoking status | Creatinine clearance/100 (mL/min) for each unit increase in blood Pb<br>−0.018 (−0.03, −0.006) |
| Pollack et al. (2015)<br><br>Buffalo, NY United States<br><br>2 menstrual cycles (8 visits per cycle) 2005–2007<br><br>Cohort | BioCycle<br>n = 259<br><br>Premenopausal women followed for 2 menstrual cycles | Blood Pb (ICP-MS) (µg/dL)<br>Median (IQR) 0.86 (0.68–1.2)<br>Mean (SD) 1.03 (0.63)<br><br>Age at Measurement: Mean (SD) 27.4 (8.2) | Creatinine and ALB<br>(BUN, $CO_2$, Chloride, Potassium, Urate, Calcium, Protein, Glucose) | Linear mixed models adjusted for age, BMI, race, average calories, alcohol intake, smoking, and cycle d | Percent Change in kidney Biomarkers per 2-fold increase in blood Pb[a]<br><br>Creatinine: 3.47 (0.85, 6.16)<br>ALB −0.38 (−1.28, 0.52)<br><br>BUN: −0.13 (−4.97, 4.96)<br>CO2: −0.57 (−1.43, 0.29)<br>Chloride: 0.20 (−0.09, 0.48)<br>Potassium: 0.01 (−1.15, 1.18)<br>Urate: 0.90 (−2.22, 4.12)<br>Calcium: −0.21 (−0.67, 0.25)<br>Protein: −0.76 (−1.61, 0.09)<br>Glucose: 0.93 (−0.28, 2.15)<br><br>*Results presented as percent change in nontransformed outcome per 2-fold increase in nontransformed exposure |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Buser et al. (2016)<br>United States<br>2007–2012<br>Cross-sectional | NHANES<br>n = 4,875<br>Pregnant and breastfeeding women were excluded | Blood Pb (ICP-MS) (µg/dL)<br>Quartiles<br>Q1 ≤ 0.79<br>Q2 0.80–1.20<br>Q3 1.21–1.82<br>Q4 > 1.82 µg/dL<br>Age at Measurement:<br>Geometric Mean 44.1 | Urinary ALB | Linear regression adjusting for age, race/ethnicity, sex, diabetes, alcohol intake, education, smoking status, body weight, hypertension, weak/failing kidney, serum cotinine, and blood cadmium | ALB (percent difference)[a]<br>Q1 Reference<br>Q2 −4.02 (−13.76, 6.93)<br>Q3 −9.24 (−19.43, 2.22)<br>Q4 6.29 (−6.39, 20.80) |
| Mujaj et al. (2019)<br>United States<br>May 2015 to September 2017<br>Cross-sectional | SPHERL<br>n = 447 men<br>Newly hired Pb workers at battery manufacturing and Pb recycling plants | Blood Pb (ICP-MS) (µg/dL)<br>Geometric mean (IQR)<br>1.66 (1.3–2.5)<br>Age at Measurement:<br>Mean (SD) 28.7 (10.2) | ACR | Linear regression adjusted for age, MAP, BMI, smoking, waist-to-hip ratio, total cholesterol to HDL ratio, plasma glucose, γ-glutamyl transferase, and antihypertensive drug treatment | Per doubling of blood Pb (mg/mmol)[a]<br>ACR:<br>−0.071 (−0.14, 0.59) |
| Jain (2019)<br>United States<br>2003–2014<br>Cross-sectional | NHANES<br>n = 25,427<br>≥20 yr | Blood Pb (ICP-MS) (µg/dL)<br>75th percentile 2.15<br>Age at measurement ≥20 yr | ACR | Logistic regression adjusting for sex, race/ethnicity, smoking status, age, BMI, survey year, fasting time, poverty income ratio, diabetes, and hypertension | OR (95% CI)[a,b]<br>ACR (≥30 mg/g creatinine)<br>1.206 (1.05, 1.385) |
| Zhu et al. (2019)<br>United States<br>2009–2012<br>Cross-sectional | NHANES<br>n = 2926<br>≥20 yr | Blood Pb (ICP-MS) (µg/dL)<br>Quartiles<br>Q1 ≤ 0.0685<br>Q2 0.0686–0.1029<br>Q3 0.1030–0.1600<br>Q4 ≥ 0.1601<br>Age at Measurement:<br>Mean (SE) 42.1 (0.46) | ACR | Linear regression adjusted for age, sex, BMI, obesity, ethnicity, education, smoking, hypertension, diabetes, and CKD | Blood Pb and continuous ACR (ln-transformed) (mg/g)[a]<br>Q1 Reference<br>Q2 0.04 (−0.06, 0.13)<br>Q3 −0.05 (−0.18, 0.08)<br>Q4 0.06 (−0.08, 0.20) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Lee et al. (2020)<br><br>United States<br><br>1999–2016<br><br>Cross-sectional | NHANES<br>n = 46,748<br><br>Adults ≥18 | Blood Pb (ICP-MS)<br>Distribution not reported<br><br>Age at Measurement:<br>Mean (SD) 47 (19) | ACR (≥30 and ≥300 mg/g) | Logistic regression adjusted for age, sex, diabetes, hypertension, BMI, race/ethnicity, smoking, and SES | Per SD of the log-transformed blood Pb concentration[a]<br><br>OR ACR (≥30 mg/g)<br>Discovery set: 1.23 (1.07, 1.42)<br>Validation set 1.08 (0.97, 1.20)<br><br>OR ACR (≥300 mg/g)<br>Discovery set: 1.39 (1.22, 1.59)<br>Validation set 1.38 (1.16, 1.63) |

ACR = albumin-to-creatinine ratio; ALB = albumin; BMI = body mass index; BUN = blood urea nitrogen; CI = confidence interval; CKD = chronic kidney disease; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; IQR = interquartile ratio; K-XRF = K-shell X-Ray Fluorescence; MAP = mean arterial pressure; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; Q = quartile; SD = standard deviation; SES = socioeconomic status; SPHERL = Study for Promotion of Health in Recycling Lead; yr = years.

*Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[a]Unable to be standardized.

[b]Increment unclear.

## Table 5–7 Animal toxicological studies of Pb exposure and albumin and creatinine.

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Zou et al. (2015) | Mouse (Control) (re-distilled water), M, n = 10<br><br>250 mg/L Pb acetate, M, n = 10 | 3-wk exposure of approximately 30-d-old mice | 250 mg/L Pb acetate or distilled water for 3 wk | 1.8 µg/dL for Control (re-distilled water)<br><br>21.7 µg/dL for 250 mg/L–PND 58 | Markers of Kidney Function: Creatinine post 3-wk exposure |
| Corsetti et al. (2017) | Mouse (Control) (Pb-free water), M, n = 8<br><br>200 ppm Pb, M, n = 8 | d 30 to d 75 | Mice were exposed to ordinary or Pb containing drinking water for 45 d | <5 µg/dL for 0 ppm<br><br>21.6 µg/dL for 200 ppm | Markers of Kidney Function: serum creatinine post 45-d exposure |
| Andjelkovic et al. (2019) | Rat (Wistar)<br>Control water, M, n = 8<br><br>150 mg/kg b.w., M, n = 6 | Single exposure by oral gavage (age of rats not reported) | Single oral dose of 150 mg/kg b.w. Pb acetate | ~25 µg/L for Control (~2.5 µg/dL)<br><br>~225 µg/L for 150 mg/kg b.w. Pb acetate (~22.5 µg/dL) | Markers of Kidney Function: serum levels of creatinine 24 hr post single exposure<br><br>Zinc and copper levels in the kidney 24 hr post single exposure |
| Shi et al. (2020) | Rat (SD)<br>Control (deionized water), M, n = 8<br><br>0.5% Pb acetate, M, n = 8 | 28 d after PND 21 | After 21 d of milk feeding, 0.5% Pb acetate or deionized water for 28 d | 0.18 ± 0.07 µg/dL for Control (deionized water)<br><br>10.21 ± 0.93 µg/dL for 0.5% Pb acetate | GFR and Markers of Kidney Function: Creatinine post exposure |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Laamech et al. (2016) | Mouse<br>Control<br>(distilled water), M/F, n = 10<br><br>5 mg/kg/d Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | Distilled water or 5 mg/kg/d Pb acetate dissolved in distilled water for 40 d | 0.009 µg/mL for control (distilled water) (0.9 µg/dL)<br><br>0.18 µg/mL for 5 mg/kg/d Pb acetate (18 µg/dL) | Markers of Kidney Function: plasma levels of creatinine 2 d post exposure |
| Gao et al. (2020) | Rat (SD)<br>Control<br>(Distilled water), M/F, n = 10<br><br>5 mg/kg Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | 5 mg/kg Pb acetate orally for 35 d followed by recovery to d 63 | <0.02 mg/kg for distilled water (<2.12 µg/dL)<br><br>0.10 ± 0.03 mg/kg for 5mg/kg Pb acetate (d 64) (10.6 ± 0.03 µg/dL) | Markers of Kidney Function: creatinine activity following the end of the experiment on d 63 |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Dumková et al. (2020b) | Mouse (Control) (clean air), F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO, F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO recovery, F, n = 10 (6 wk PbO, 5 wk clean air) | Age of mice in experiment unclear | PbO 78.0 µg PbO/$m^3$ or clean air for 24 hr/d 7 d/wk for 2 wk, 6 wk, or 11 wk. a recovery group was exposed to PbO for 6 wk and then clean air for 5 wk (11 wk total) | <3 ng/g in control (2 wk, 6 wk, 11 wk) (0.3 µg/dL)<br><br>104 ng/g PbO 2 wk (10.4 µg/dL)<br><br>148 ng/g PbO 6 wk (14.8 µg/dL)<br><br>174 ng/g PbO 11wk (17.4 µg/dL) | Markers of Kidney Function: Creatinine at 2 wk, 6 wk, and 11 wk |

d = days; GFR = glomerular filtration rate; hr = hours; F = female; M = male; M/F = male/female; Pb = lead; PbO = Pb oxide; PND = postnatal day; SD = standard deviation; wk = weeks.

## Table 5–8 Epidemiologic studies of Pb exposure and uric acid.[a]

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis |
|---|---|---|---|---|---|
| Park and Kim (2021)<br><br>South Korea<br><br>2016–2017<br><br>Cross-sectional | KNHANES n = 4,784<br><br>Participants ≥20 | Blood Pb (GFAAS) (µg/dL)<br>Geometric mean:<br>Overall, 1.69<br>Men 1.95<br>Women 1.50<br><br>Age at measurement ≥20 | SUA and hyperuricemia (SUA >7.0 mg/dL in men and >6.0 mg/dL in women) | Linear and logistic regression adjusting for age, residence area, education level, smoking status, drinking status, physical activity, hypertension, glucose, triglyceride, cholesterol, eGFR, blood cadmium and blood mercury | Per doubling of Blood Pb<br>Log SUA (mg/dL)<br>Men: −0.018 (−0.038, 0.002)<br>Women: 0.019 (0.001, 0.037)<br><br>Hyperuricemia (OR) per doubling of blood Pb[a]<br>Men: 0.928 (0.718, 1.198)<br>Women: 1.095 (0.727, 1.649) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis |
|---|---|---|---|---|---|
| Arrebola et al. (2019)<br><br>Spain<br>2009–2010<br>Cross-sectional | BIOAMBIENT.ES study<br>n = 882<br>458 males and 424 females | Blood Pb (method not indicated) (µg/dL)<br><br>Median 0.106<br>75th 0.181<br>90th 0.284<br>95th 0.355<br><br>Age at measurement<br>Median 35.4–38.1 | UA and hyperuricemia (UA > 7.0 mg/dL in males or >6.0 mg/dL in females, prescribed any medication for lowering UA levels, diagnosis of gout by a physician) | logistic or linear regression adjusting for sex, age, weight loss in past 6 mo, smoking status, alcohol consumption, education, region of recruitment, place of residence | Per 1 unit increase in log-transformed Pb<br><br>Log SUA (mg/dL)<br>5.95 (−0.02, 0.05)<br><br>Hyperuricemia (OR)<br>1.12 (0.90, 1.41) |
| Jung et al. (2019)<br><br>South Korea<br>2016 | KNHANES<br>n = 2,682<br>1124 men and 1528 women) aged ≥19 yr | Blood Pb (GFAAS) (µg/dL)<br><br>Hyperuricemia<br>Median (IQR) 2.04 (1.59–2.51)<br>No Hyperuricemia<br>Median (IQR) 1.73 (1.34–2.28)<br><br>Age at measurement<br>Hyperuricemia<br>Mean (SE) 46.4 (1.3)<br>No hyperuricemia<br>Mean (SD) 46.9 (0.5) | Hyperuricemia (SUA >7.0 mg/dL in men and >6.0 mg/dL in women) | Logistic regression adjusting for age, BMI, eGFR, residence, education, smoking status, alcohol consumption, physical activity, and blood pressure | See Figure 5-5 |

BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; IQR = interquartile ratio; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; KNHANES = Korea National Health and Nutrition Examination Survey; mo = months; OR = odds ratio; SD = standard deviation; SE = standard error; SUA = serum uric acid; UA = uric acid; yr = years.

[a]Unable to be standardized.

## Table 5–9 Animal toxicological studies of Pb exposure and measures of uric acid and urea.

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Zou et al. (2015) | Mouse (Control) (re-distilled water), M, n = 10<br><br>250 mg/L Pb acetate, M, n = 10 | 3-wk exposure of approximately 30-d-old mice | 250 mg/L Pb acetate or distilled water for 3 wk | 1.8 µg/dL for Control (re-distilled water)<br><br>21.7 µg/dL for 250 mg/L–PND 58 | Markers of Kidney Function: BUN post 3-wk exposure |
| Andjelkovic et al. (2019) | Rat (Wistar)<br>Control water, M, n = 8<br><br>150 mg/kg b.w., M, n = 6 | Single exposure by oral gavage (age of rats not reported) | Single oral dose of 150 mg/kg b.w. Pb acetate | ~25 µg/L for Control (~2.5 µg/dL)<br><br>~225 µg/L for 150 mg/kg b.w. Pb acetate (~22.5 µg/dL) | Markers of Kidney Function: serum levels of BUN 24 hr post single exposure<br><br>Zinc and copper levels in the kidney 24 hr post single exposure |
| Shi et al. (2020) | Rat (SD)<br>Control (deionized water), M, n = 8<br><br>0.5% Pb acetate, M, n = 8 | 28 d after PND 21 | After 21 d of milk feeding, 0.5% Pb acetate or deionized water for 28 d | 0.18 ± 0.07 µg/dL for Control (deionized water)<br><br>10.21 ± 0.93 µg/dL for 0.5% Pb acetate | Markers of Kidney Function: BUN and UA post exposure |
| Carlson et al. (2018) | Mouse (Control) (water), M/F, n = 16<br><br>0.03 mM Pb, M/F, n = 8 | Treatment began no earlier than an age of 5 wk for 11 wk | Pb free water or 0.03 mM Pb acetate dissolved in drinking water for 11 wk | Control (water) not detected<br><br>2.89 ± 0.44 µg/dL for 0.03 mM | Markers of Kidney Function: BUN 1 wk after 11-wk exposure |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Laamech et al. (2016) | Mouse<br>Control (distilled water), M/F, n = 10<br><br>5 mg/kg/d Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | Distilled water or 5 mg/kg/d Pb acetate dissolved in distilled water for 40 d | 0.009 µg/mL for control (distilled water) (0.9 µg/dL)<br><br>0.18 µg/mL for 5 mg/kg/d Pb acetate (18 µg/dL) | Markers of Kidney Function: plasma levels of urea and UA 2 d post exposure |
| Gao et al. (2020) | Rat (SD)<br>Control (Distilled water), M/F, n = 10<br><br>5 mg/kg Pb acetate, M/F, n = 10 | Age of mice in experiment not reported | 5 mg/kg Pb acetate orally for 35 d followed by recovery to d 63 | <0.02 mg/kg for distilled water (< 2.12 µg/dL)<br><br>0.10 ± 0.03 mg/kg for 5 mg/kg Pb acetate (d 64) (10.6 ± 0.03 µg/dL) | Markers of Kidney Function: BUN activity following the end of the experiment on d 63 |
| Dumková et al. (2020b) | Mouse (Control) (clean air), F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO, F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO recovery, F, n = 10 (6 wk PbO, 5 wk clean air) | Age of mice in experiment unclear | PbO 78.0 µg PbO/$m^3$ or clean air for 24 hr/d 7 d/wk for 2 wk, 6 wk, or 11 wk. a recovery group was exposed to PbO for 6 wk and then clean air for 5 wk (11 wk total) | <3 ng/g in control (2 wk, 6 wk, 11 wk) (0.3 µg/dL)<br><br>104 ng/g PbO 2 wk (10.4 µg/dL)<br><br>148 ng/g PbO 6 wk (14.8 µg/dL)<br><br>174 ng/g PbO 11wk (17.4 µg/dL) | Markers of Kidney Function: Urea at 2, 6, and 11 wk |

BUN = blood urea nitrogen; d = days; F = female; hr = hours; M = male; M/F = male/female; Pb = lead; PbO = Pb oxide; SD = standard deviation; wk = weeks.

## Table 5–10 Epidemiologic studies of Pb exposure and proteinuria and hematuria.

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Chung et al. (2014)<br><br>South Korea<br>2008<br><br>Cross-sectional | KNHANES<br>n = 2,005<br><br>≥20 yr with data for blood Pb and cadmium. Pregnant women were excluded | Blood (GFAAS with Zeeman correction) (µg/dL)<br>Geometric mean: 2.5<br>Quartiles (Mean)<br>Q1 1.38<br>Q2 2.10<br>Q3 2.74<br>Q4 4.13<br><br>Age at Measurement:<br>Mean (Range) 46 (20–87) | Proteinuria | Linear regression adjusted for age, sex, smoking, hypertension, or diabetes.<br>Logistic regression adjusted for age, sex, smoking hypertension, BMI, and blood cadmium | OR (95% CI) (Q4 vs. Q1, per 1 µg/dL increase in blood Pb)<br><br>1.08 (1.00, 1.16) |
| Han et al. (2013)<br><br>South Korea<br><br>2008–2010<br><br>Cross-sectional | KNHANES<br>n = 4,701 | Blood (GFAAS with Zeeman correction) (µg/dL)<br>Geometric mean: 1.08<br>Quartiles<br>Q1 < 1.89<br>Q2 1.89–2.46<br>Q3 2.47–3.22<br>Q4 > 3.22<br><br>Age at Measurement:<br>Mean 50 yr | Hematuria | Logistic regression adjusting for age, sex, residential region, education level, and anemia | OR (95% CI)[a]<br>Q1 Reference<br>Q2 1.00 (0.767, 1.303)<br>Q3 0.90 (0.687, 1.178)<br>Q4 0.94 (0.701, 1.253) |

BMI = body mass index; BUN = blood urea nitrogen; CI = confidence interval; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; KNHANES = Korea National Health and Nutrition Examination Survey; OR = odds ratio; Q = quartile; yr = years.

*Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[a]Unable to be standardized.

## Table 5–11 Epidemiologic studies of Pb exposure and renal tubular impairment markers.[a]

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis |
|---|---|---|---|---|---|
| Lim et al. (2016)<br><br>South Korea<br>2010–2012<br><br>Cross-sectional | KRIEFS<br>n = 1953<br><br>participants > 19 without kidney disease | Blood Pb (GFAAS) (µg/dL)<br>Geometric mean 2.21<br><br>Age at Measurement<br>Mean 45.5 | Renal tubular impairment (NAG and $\beta_2$-MG) | Linear regression adjusting for age, sex, BMI, household income, smoking, alcohol consumption, hypertension, and diabetes | Log-transformed Pb<br><br>NAG (Unit/g creatinine)<br>0.09 (−0.05, 0.23)<br><br>$\beta_2$-MG (µg/g creatinine)<br>0.01 (−0.13, 0.15) |
| Jung et al. (2016)<br><br>Jangseong-gun South Korea<br><br>June–August 2013 and August–November 2014<br>Cross-sectional | n = 547<br><br>Participants living near cement plant | Blood Pb (AAS [flameless method]) (µg/dL)<br><br>Quartiles<br>Q1 0.77–2.13<br>Q2 2.13–2.70<br>Q3 2.70–3.50<br>Q4 3.50–10.37<br><br>Age at Measurement:<br>Mean (SD) 64.32 (11.02) | Renal tubular impairment (NAG > 5.67 U/L) | Logistic regression adjusting for sex, age, occupation, smoking, air pollution exposure, hypertension, diabetes, urine cadmium, urine mercury | Renal tubular impairment<br>OR (95% CI)<br>Q1 Reference<br>Q2 0.96 (0.49, 1.87)<br>Q3 0.89 (0.44, 1.77)<br>Q4 0.67 (0.32, 1.41) |

AAS = Atomic Absorption Spectrometry, $\beta_2$-MG = $\beta_2$-microglobulin; BMI = body mass index; CI = confidence interval; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; KRIEFS = Korean Research Project on the Integrated Exposure Assessment to Hazardous Materials for Food Safety; NAG = acetyl-β-D-glucosaminidase; OR = odds ratio; Q = quartile; SD = standard deviation.

[a]Unable to be standardized.

## Table 5–12 Animal toxicological studies of Pb exposure and other markers of kidney function.

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Andjelkovic et al. (2019) | Rat (Wistar)<br>Control water, M, n = 8<br><br>150 mg/kg b.w., M, n = 6 | Single exposure by oral gavage (age of rats not reported) | Single oral dose of 150 mg/kg b.w. Pb acetate | ~25 µg/L for Control (~2.5 µg/dL)<br><br>~225 µg/L for 150 mg/kg b.w. Pb acetate (~22.5 µg/dL) | Total protein, zinc, and copper levels in the kidney 24 hr post single exposure |
| Fioresi et al. (2014) | Rat (Wistar)<br>Control (tap water), M, n = 9–12<br><br>100 ppm group, M, n = 9–12 | Age 2 mo to 3 mo | 100 ppm Pb acetate in drinking water for 30 d | <0.5 µg/dL for control<br><br>13.6 ± 1.07 µg/dL for 100 ppm group | ACE activity measured post 30-d exposure |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Dumková et al. (2020a) | Mouse (Control) (clean air), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk)<br><br>Pb(NO3)2 (68.6 µg/m^3), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk)<br><br>Recovery (Pb(NO3)2 68.6 µg/m$^3$), F, n = 10 (6 wk Pb/5 wk recovery) | 6–8 wk old mice exposed for 3 d, 2 wk, 6 wk, or 11 wk | Pb (NO3)2 (68.6 µg/m$^3$) or clean air-exposed mice for 3 d, 2 wk, 6 wk, or 11 wk. To assess recovery a separate group of mice were exposed for 11 wk followed by 5 wk of clean air | <0.3 ng/g for control at all timepoints (<0.3 µg/dL) (d 3, 2 wk, 6 wk, 11 wk)<br><br>31 ng/g for Pb(NO3)2 d 3 (3.1 µg/dL)<br><br>40 ng/g for Pb(NO3)2 2 wk (4.0 µg/dL)<br><br>47 ng/g for Pb(NO3)2 6 wk (4.7 µg/dL)<br><br>85 ng/g for Pb(NO3)2 11 wk (8.5 µg/dL)<br><br>10 ng/g for Pb(NO3)2 exposure 6 wk and clean air for 5 wk (1.0 µg/dL) | Total protein, calcium, sodium, and potassium levels in the kidney post 3 d, 2 wk, 6 wk, 11 wk, and 11 wk plus clearance for 5 wk (~16 wk) |

| Study | Species (Stock/Strain), n, Sex | Timing of Exposure | Exposure Details (Concentration, Duration) | BLL as Reported (µg/dL) | Endpoints Examined |
|---|---|---|---|---|---|
| Dumková et al. (2020b) | Mouse (Control) (clean air), F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO, F, n = 10 (2 wk, 6 wk, 11 wk)<br><br>PbO recovery, F, n = 10 (6 wk PbO, 5 wk clean air) | Age of mice in experiment unclear | PbO 78.0 µg PbO/$m^3$ or clean air for 24 hr/d 7 d/wk for 2 wk, 6 wk, or 11 wk. A recovery group was exposed to PbO for 6 wk and then clean air for 5 wk (11 wk total) | <3 ng/g in control (2 wk, 6 wk, 11 wk) (0.3 µg/dL)<br><br>104 ng/g PbO 2 wk (10.4 µg/dL)<br><br>148 ng/g PbO 6 wk (14.8 µg/dL)<br><br>174 ng/g PbO 11 wk (17.4 µg/dL) | Total protein post 2 wk, 6 wk, and 11 wk exposure |

d = days; hr = hours; F = female; M = male; PbO = Pb oxide; wk = weeks.

## Table 5–13 Epidemiologic studies of Pb exposure and renal outcomes in children.

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Fadrowski et al. (2010)<br><br>1988–1994<br><br>Cross-sectional | NHANES III<br>n = 769<br>Adolescents aged 12–20 | Whole blood Pb (GFAAS) (µg/g)<br><br>Median (IQR) 1.5 (0.7, 2.9)<br>Quartile<br>Q1 < 1.0<br>Q2 1.0–1.5<br>Q3 1.6–2.9<br>Q4 > 2.9<br><br>Age at measurement<br>12–15 46%<br>16–20 54% | eGFR (cystatin C and serum creatinine-based estimates) | Linear regression adjusted for age, sex, race/ethnicity, urban vs. rural residence, tobacco smoke exposure, obesity, annual household income, and educational level of the family reference person | eGFR (mL/min/1.73 $m^2$), compared with referent (Q1)[a]<br><br>Cystatin C-based<br>Q2 −1.4 (−7.4, 4.5)<br>Q3 −2.6 (−7.3, 2.2)<br>Q4 −6.6 (−12.6, −0.7)<br><br>Creatinine-based<br>Q2 −0.5 (−6.1, 5.1)<br>Q3 −1.7 (−6.9, 3.5)<br>Q4 −1.9 (−7.4, 3.5) |
| Skröder et al. (2016)<br><br>Bangladesh<br><br>June 2002–June 2004<br><br>Cohort | Maternal and Infant Nutrition Interventions, Matlab<br>n = 1,511 (GW14); 713 (GW30)<br><br>Mother-child pairs | Erythrocyte Pb (ICP-MS followed by dilution in alkali solution (GW14) or acid digestion (GW30)) (µg/g)<br><br>GW14<br>Median (95th) 73 (172)<br>GW30<br>Median (95th) 86 (506)<br><br>Age at Measurement: Mean (SD) 26 (6) (age of mothers) | Kidney volume, eGFR, serum cystatin C<br><br>Blood pressure in children<br><br>Age at outcome 4.5 yr | Linear regression adjusted for gender, birth weight, season of birth, age at outcome measurements, height for age Z-score, maternal BMI at GW8, parity, SES, and supplementation group | Per µg/kg Eyr-Pb[a]<br><br>GW14<br>Kidney volume ($cm^3/m^2$) 0.062 (−0.36, 0.24)<br>eGFR (mL/min/1.73 $m^2$) 0.089 (−0.012,0.30)<br>Serum cystatin C (mg/L)<br>−0.00088 (−0.0028, 0.001)<br><br>GW30<br>Kidney Volume ($cm^3/m^2$)<br>−0.071 (−1.4, −0.030)<br>eGFR (mL/min/1.73 $m^2$) 0.71 (−0.24,0.17)<br>Serum cystatin C (mg/L)<br>0.000027 (−0.0018, 0.0018) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Fadrowski et al. (2013)<br><br>United States and Canada<br><br>2007–2009<br><br>Cross-sectional | CkiD<br>n = 391 (485 Pb measurements)<br><br>Children with CKD (1–16 yr of age) | Whole blood Pb (high resolution ICP-MS) (µg/dL)<br>Median (Range) 1.2 (0.2–6.2)<br><br>Age at measurement<br>0–5 13%<br>6–11 38%<br>12–19 49% | GFR<br><br>GFR directly measured at yr 2 and 4 of CkiD study | Linear regression adjusted for age, sex, race, ethnicity, BMI, poverty, CKD diagnosis (glomerular or nonglomerular), urine protein to creatinine ratio, and ln-transformed blood cadmium | Change (mL/min/1.73 $m^2$) in GFR<br>−0.9 (−2.6, 0.8)<br><br>Percent change in GFR<br>Total sample −2.1 (−6.0, 1.8)<br>With glomerular CKD −12.1 (−22.2, −1.9)<br>With nonglomerular CKD −0.7 (−4.8, 3.4) |
| Cárdenas-González et al. (2016)<br><br>San Luis Potosi Mexico<br><br>2014<br><br>Cross-sectional | n = 83<br><br>Children attending 2 elementary schools in San Luis Potosi, Mexico | Whole blood Pb (GFAAS) (µg/dL)<br><br>Geometric mean (Range)<br>5.95 (1.47–26.89)<br><br>Age at Measurement Mean (SD) 8.13 (1.93) | Kidney Injury Molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) | Linear regression adjusted for age, sex, BMI, urinary specific gravity, or urinary creatinine | No associations between blood Pb and kidney injury biomarkers (data not shown) |

| Reference and Study Design | Study Population | Exposure Assessment | Outcome | Confounders | Effect Estimates and 95% Cis* |
|---|---|---|---|---|---|
| Hu et al. (2019)<br><br>United States<br><br>1999–2006<br><br>Cross-sectional | NHANES<br>n = 8,303<br><br>Adolescents aged 12–19 | Blood Pb (AAS with Zeeman correction) (µg/dL)<br>Mean: 1.3<br><br>Age at Measurement<br>Mean (SD) 15.5 (2.3) | SUA | Linear regression adjusted age, sex, BMI, race, education status, hemoglobin, HDL-C, and eGFR | Per 1 unit increase in ln-transformed blood Pb[a]<br>SUA (mg/dL) 0.14 (0.10, 0.17)<br><br>OR (SUA ≥ 5.5 mg/dL) 1.29 (1.17, 1.42) |

AAS = Atomic Absorption Spectrometry; BMI = body mass index; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children; eGFR = estimated glomerular filtration rate; GFAAS = Graphite Furnace Atomic Absorption Spectrometry; GFR = glomerular filtration rate; GW = gestation week; HDL-C = high-density lipoprotein cholesterol; ICP-MS = Inductively Coupled Plasma Mass Spectrometry; IQR = interquartile ratio; KIM-1 = kidney injury molecule 1; NGAL = neutrophil gelatinase-associated lipocalin; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; Q = quartile; SD = standard deviation; SES = socioeconomic situation; SUA = serum uric acid; UA = uric acid; yr = years.

*Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th-90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[a]Unable to be standardized.

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