6.4 RENAL EFFECTS OF LEAD

6.4.1 Summary of Key Findings on the Renal Effects of Lead from the 1986 Lead AQCD

Chronic Pb nephropathy is a disease characterized by tubulointerstitial nephritis, which can ultimately result in small, fibrotic kidneys. It occurs in individuals who sustain chronic high-level Pb exposure. In these individuals, Pb exposure is the primary cause of renal failure. The pathophysiologic characteristics of Pb nephropathy and the populations at increased risk for this diagnosis were the foci of the human research portion of Section 12.5, entitled "Effects of Lead on the Kidney," in the 1986 Lead AQCD. The 1986 document clearly identified several high-risk groups for this diagnosis, including children in the Queensland, Australia Pb poisoning epidemic, moonshine alcohol drinkers, and Pb workers in poorly controlled settings. The section concluded that data in the latter group indicated an increased risk for Pb nephropathy associated with blood Pb levels ranging from 40 to >100 μg/dL, with adverse renal effects possibly occurring at levels as low as 30 μg/dL.

The 1986 Lead AQCD noted that research at that time was not sufficient to address some of the most critical questions relating to the impact of Pb exposure on the kidney. The last paragraph of the renal section begins with "Among the questions remaining to be answered more definitively about the effects of Pb on the kidneys is the lowest blood Pb level at which renal effects occurs." The last sentence reads "Conversely, the most difficult question of all may well be to determine the contribution of low levels of Pb exposure to renal disease of non-Pb etiologies." Advances in the research conducted since that document was written allow a much more informed discussion of exactly those critical issues. As discussed below, recent research indicates that Pb nephropathy is merely the tip of the iceberg in terms of the contribution that Pb makes to renal dysfunction overall. Research increasingly indicates that Pb, at much lower doses than those causing Pb nephropathy, acts as a cofactor with other more established renal risks to increase the risk for renal dysfunction and the rate of subsequent decline. The populations at risk for renal dysfunction (diabetics and hypertensives) are increasing worldwide, particularly in countries where obesity is epidemic. Pb exposure is declining in many industrialized countries, although less so among high-risk minority populations. The extent of the public health impact of Pb on the kidney depends on the balance of these two factors.

6.4.2 Renal Outcome Definitions

The renal literature can be confusing, because several of the clinical renal measures are inversely related. Therefore, the pertinent outcomes are briefly reviewed below. The glomerular filtration rate (GFR) is considered to be the best measure of renal function. GFR is assessed by urinary clearance of exogenous (e.g., ^{125}I-iothalamate) or endogenous (e.g., blood urea nitrogen [BUN] and serum creatinine) compounds. Creatinine is used most commonly. Therefore, increases in BUN or serum creatinine or decreases in renal clearance of creatinine or other markers are all consistent with decreased renal function. Serum creatinine and its reciprocal have been the most frequently used measures of renal function in the Pb-kidney literature. However, creatinine is not an ideal GFR marker, because it is influenced by factors such as muscle mass, diet, gender, age, and tubular secretion. Measurement or calculation of creatinine clearance takes some of these variables into account. Measured creatinine clearance utilizes timed urine collections, traditionally over a 24-h period, making compliance difficult. Therefore, equations to estimate creatinine clearance have gained popularity. The Cockcroft-Gault equation (Cockcroft and Gault, 1976) has been used most commonly. Recently, several equations to estimate actual GFR were studied in the Modification of Diet in Renal Disease (MDRD) Study (Levey et al., 1999). The abbreviated MDRD equation (GFR in mL/min/1.73m^2 = 186 $\times$ creatinine$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ (0.742 if female) $\times$ (1.212 if African-American); Stevens and Levey [2005a]) estimates GFR more accurately than the Cockcroft-Gault equation in patients with renal insufficiency (Levey et al., 2003). Despite their promise, however, the MDRD equations are relatively new and their use in studies of renal effects of Pb exposure has been limited to date.

Cystatin C is another recent addition to the tools used to assess GFR (Stevens and Levey, 2005b). This is a 13,000 Dalton, non-glycosylated basic protein, which is generated by all nucleated cells and filtered, reabsorbed, and catabolized, but not secreted, in the kidney. Very little appears in the urine. The majority of studies done to date indicate that serum cystatin C is a better marker for GFR than serum creatinine (Stevens and Levey, 2005b).

Most of the renal outcome measures discussed above were developed for use in the clinical setting. Unfortunately, they are insensitive for early renal damage, as evidenced by the fact that serum creatinine remains normal after kidney donation. Therefore, in the last two decades, the utility of renal early biological effect (EBE) markers as indicators of preclinical renal damage has been of interest. These can be categorized as markers of function (i.e., low

molecular weight proteins that should be reabsorbed in the proximal tubules such as β_2-microglobulin and retinol-binding protein [RBP]); biochemical alteration (i.e., urinary eicosanoids such as prostaglandin E_2, prostaglandin $F_{2\ alpha}$, 6-keto-prostaglandin $F_{1\ alpha}$, and thromboxane B_2); and cytotoxicity (e.g., N-acetyl-β-D-glucosaminidase [NAG]) (Cárdenas et al., 1993). Elevated levels may indicate an increased risk for subsequent renal dysfunction. However, with the exception of microalbuminuria in diabetes and β_2-microglobulin in Cd exposure, most are research tools only, and their prognostic value remains controversial. Asian and European nephrotoxicant researchers have used them more frequently than have U.S. renal researchers. Prospective studies of most of these markers in nephrotoxicant-exposed populations are quite limited to date.

6.4.3 Lead Exposure Measure Definitions

Although these definitions are reviewed in detail elsewhere in this Lead AQCD, a brief discussion is included here due to the number of key studies in this section that measured bone or chelatable Pb dose. Inorganic Pb is a cumulative toxicant that is stored in bone. Blood Pb is a relatively short-term measure (half-life of 30 days [Hu et al., 1998]) that reflects exposure from current exogenous sources and the release of Pb from internal Pb stores. Bone is an internal source of Pb as well as a repository (Hu et al., 1998). As such, bone Pb measures provide an index not only of cumulative Pb exposure but also the potential for ongoing internal exposure, as well. Lead in trabecular bone (commonly measured in the patella or calcaneus) is more bioavailable than Pb in cortical bone (measured in the mid-tibia) and has a shorter half-life (Gerhardsson, et al., 1993; Hu et al., 1998). An additional Pb measure, chelatable Pb, is thought to represent a bioavailable pool of Pb from blood, soft tissue, and bone. Two chelation agents, either calcium disodium ethylenediaminetetraacetic acid (EDTA) or dimercaptosuccinic acid (DMSA; succimer) have mainly been used for this purpose, although DMSA is newer and, thus, used less frequently to date.

6.4.4 Lead Nephrotoxicity in Adults

6.4.4.1 General Population Studies

Over the past two decades, several studies have examined the effect of Pb exposure on renal function in general populations. This is a new category of Pb-renal research. No high

quality examples (by current standards) were available for review in the 1986 Lead AQCD. The studies discussed below provide critical evidence that the adverse effects of Pb on the kidney occur at much lower doses than previously appreciated. Traditional renal function measures, such as serum creatinine, BUN and creatinine clearance, are emphasized below, since much more is known regarding the clinical relevance of these measures than for the renal EBE markers. General population studies of the renal effects of Pb are further summarized in Annex Table AX6-4.1.

6.4.4.1.1 Cadmibel Study

In the first large environmental study that adjusted for multiple renal risk factors, Staessen et al. (1992) evaluated 965 men and 1,016 women in the Belgian Cadmibel study. Lead dose was indexed by blood Pb and zinc protoporphyrin. Renal outcome measures included (a) serum creatinine and β_2-microglobulin and (b) 24-h measured and calculated (Cockcroft and Gault, 1976) creatinine clearances. Mean blood Pb was 11.4 μg/dL (range 2.3-72.5) and 7.5 μg/dL (range 1.7-60.3) in men and women, respectively. After adjustment, log transformed blood Pb and zinc protoporphyrin, in separate models, were negatively associated with measured creatinine clearance. A 10-fold increase in blood Pb was associated with a decrease in creatinine clearance of 10 and 13 mL/min in men and women, respectively. Both Pb measures were also negatively associated with estimated creatinine clearance. This landmark study raised concern that the Pb dose threshold for adverse renal effects in the general population might be much lower than had been previously appreciated based on occupational exposure data.

6.4.4.1.2 Normative Aging Study

Research in the Normative Aging Study population reached similar conclusions. Four studies assessing the renal impact of Pb exposure in this population have thus far been published. Participants in this study were originally recruited in the 1960s in the Greater Boston area. Inclusion criteria included male gender, age 21 to 80 years, and absence of chronic medical conditions. Payton et al. (1994) analyzed data from a periodic follow-up evaluation performed between 1988 and 1991 in 744 participants. Lead dose was indexed by blood Pb; renal outcome measures included serum creatinine and 24-h measured and calculated (Cockcroft and Gault, 1976) creatinine clearances. Mean blood Pb concentration and measured creatinine clearance

were 8.1 μg/dL (SD 3.9) and 88.2 mL/min (SD 22.0), respectively. After adjustment, ln blood Pb was negatively associated with ln measured creatinine clearance (β = −0.04 [95% CI: −0.079, −0.001]). Borderline statistically significant associations ($p < 0.1$) between blood Pb and serum creatinine and estimated creatinine clearance were also observed. Kim et al. (1996) studied 459 men whose blood Pb levels from past periodic examinations, conducted every 3 to 5 years during 1979-1994, were measured from stored samples. Participants were randomly selected to be representative of the entire Normative Aging Study population in terms of age and follow-up. Renal status was assessed with serum creatinine. Data from 4 to 5 evaluations were available for the majority of participants. Relations were evaluated cross-sectionally (associations between blood Pb and concurrent serum creatinine) as well as longitudinally (associations between blood Pb and change in serum creatinine over the subsequent follow-up period). Mean age, blood Pb level, and serum creatinine, at baseline, were 56.9 years (SD 8.3), 9.9 μg/dL (SD 6.1), and 1.2 mg/dL (SD 0.2), respectively. With random-effects modeling, a significant positive association between ln-transformed blood Pb and concurrent serum creatinine was observed. This association was stronger when models were confined to participants with lower peak blood Pb levels, i.e., the β coefficient was largest in the 141 participants whose highest blood Pb level was ≤10 μg/dL (β = 0.06 [95% CI: 0.023, 0.097]). In the longitudinal analysis, ln-transformed blood Pb was associated with change in serum creatinine over the subsequent follow-up period in the 428 participants whose highest blood Pb level was ≤25 μg/dL (β = 0.027 [95% CI: 0.0, 0.054]). Similar to the cross-sectional analysis, the β coefficient in the participants whose highest blood Pb level was ≤10 μg/dL was larger; however, in the longitudinal analysis, the standard error also increased such that the p-value was not significant.

Cortical and trabecular bone Pb measurements were obtained in evaluations performed between 1991 and 1995 in 709 participants in the Normative Aging Study (Wu et al., 2003a). Lead dose was assessed with blood, tibia, and patella Pb concentrations. Renal outcome measures included serum creatinine and estimated creatinine clearance. Mean blood, tibia and patella Pb levels were 6.2 μg/dL (SD 4.1), 22.0 μg/g bone mineral (SD 13.4), and 32.1 μg/g bone mineral (SD 19.5), respectively. After adjustment, analyses in the 670 participants from whom these data were available, revealed a significant inverse association between patella Pb and creatinine clearance (β = −0.069 [SE not provided]). A borderline significant ($p = 0.08$) inverse

association between tibia Pb and creatinine clearance was also observed. None of the Pb measures were significantly associated with serum creatinine.

Tsaih et al. (2004) reported associations between baseline Pb dose and change in serum creatinine in 448 men. Lead dose was assessed in terms of blood, tibia, and patella Pb. Serum creatinine was measured at baseline and at follow-up, an average of 6 years later. Six percent and 26% of subjects had diabetes and hypertension, at baseline, respectively. Mean blood Pb levels and serum creatinine decreased significantly over the follow-up period in the group. Lead dose was not associated with change in creatinine in all participants. However, a significant interaction was found between blood and tibia Pb and diabetes on change in serum creatinine. For ln blood Pb, $\beta = 0.076$ (95% CI: 0.031, 0.121) in diabetics compared to $\beta = 0.006$ (95% CI: −0.004, 0.016) in non-diabetics. A similar relationship was observed for tibia Pb. An interaction was also observed between tibia Pb and hypertension, although it is possible that many of the 26 diabetics were also included in the hypertensive group and were influential there as well.

6.4.4.1.3 NHANES III

Muntner et al. (2003) analyzed associations between blood Pb and renal outcomes in 15,211 adult subjects enrolled in the NHANES III study, conducted from 1988 through 1994. Dichotomous renal outcome measures analyzed included elevated serum creatinine and chronic kidney disease (GFR < 60mL/min/1.73 m^2). Due to an interaction between blood Pb and hypertension, the population was stratified. Mean blood Pb level was 4.21 μg/dL in the 4,813 hypertensives and 3.30 μg/dL in normotensives. The prevalence of elevated serum creatinine in hypertensives and nonhypertensives was 11.5% and 1.8%, respectively, but the prevalence of chronic kidney disease was similar. The odds ratios for both renal outcomes increased by quartile of blood Pb among the hypertensive subjects but not among those without hypertension. Among those with hypertension, after adjustment for age, race and gender, the odds ratios for elevated creatinine in quartiles 2, 3, and 4 compared to the lowest quartile of blood Pb, were 1.56 (95% CI: 1.04, 2.35), 1.68 (95% CI: 1.24, 2.26), and 2.07 (95% CI: 1.26, 3.40), respectively. The odds ratios were the same following additional adjustment. The authors noted that the "associations were strong, dose-dependent and consistent before and after comprehensive adjustment." They also noted that in nonhypertensives, higher blood Pb was associated with a higher prevalence of chronic kidney disease in diabetics. This study is notable

for sample size, comprehensive adjustment for other renal risk factors, and the fact that this study population is representative of the U.S. non-institutionalized, civilian population.

6.4.4.1.4 Women's Health in the Lund Area Study

In a study of 820 women (age 53 to 64 years) in Sweden, significant negative associations were observed between blood Pb and both GFR (estimated from serum cystatin C) and creatinine clearance (estimated by the Cockcroft-Gault equation [Cockcroft and Gault, 1976]) (Akesson et al., 2005). Mean blood Pb was only 2.2 μg/dL; the association was apparent over the entire dose range (Akesson, 2006). This study has the additional advantage of blood and urinary Cd assessment.

6.4.4.1.5 Summary of Lead-Related Nephrotoxicity in the General Population

General population studies constitute one of the two most important types of research on the renal effects of Pb during the past two decades. Overall, a number of strengths are present in this body of literature. These include study design with longitudinal data in some studies; large populations in both Europe and the United States; comprehensive assessment of Pb dose, including the use of bone Pb as a measure of cumulative Pb body burden in some studies; and statistical approaches that utilize a range of exposure and outcome measures, while adjusting for numerous renal risk factors. Associations between Pb dose and worse renal function were observed in most of the general population studies.

Threshold for Lead-Related Nephrotoxicity

Increased risk for nephrotoxicity has been observed at the lowest Pb dose levels studied to date. Specifically, blood Pb ranged from 2.5 to 3.8 μg/dL in the first significant category in Muntner et al. (2003), and associations between blood Pb as a continuous variable and worse renal function have been reported at a mean of 2.2 μg/dL (Akesson et al., 2005). An association between cumulative Pb dose (mean tibia Pb of 21.5 μg/g bone mineral) and longitudinal decline in renal function has been observed as well, although data on any threshold for this effect were not reported (Tsaih et al., 2004). The data available to date are not sufficient to determine whether nephrotoxicity is related more to current blood Pb levels, higher levels from past Pb

exposures, or both. However, Kim et al. (1996) noted associations in participants whose peak blood Pb levels were ≤10 μg/dL as far back as 1979.

Alternative Explanations for Observed Associations

Potential residual confounding as a possible explanation for associations between Pb dose and adverse health effect outcomes is always a consideration. One general population study provided data useful to address this concern in the Pb-renal literature. For both renal outcomes assessed, Muntner et al. (2003) observed that the odds ratios in hypertensives initially adjusted for age, race, and gender, increased further after additional adjustment for diabetes, systolic blood pressure, smoking status, history of cardiovascular disease, body mass index, alcohol consumption, household income, education level, marital status, and health insurance. In contrast, after adjustment, regression coefficients decreased in Wu et al. (2003b). However, the analyses were performed in slightly different populations, making interpretation of the adjustment differences less certain. Further, as noted in the Agency for Toxic Substances and Disease Registry's Draft Toxicological Profile For Lead ([2005] Atlanta, GA: U.S. Department of Health and Human Services), since increased blood pressure is associated with Pb dose in general populations, adjustment for hypertension or blood pressure, although extremely common in Pb-renal studies, risks underestimating the actual slope of the association between Pb dose and renal dysfunction. Overall, one of the strengths of the Pb-renal general population literature is the number of factors adjusted for. Thus, residual confounding is an unlikely explanation for observed associations.

Reverse causality has also been considered as a possible explanation for associations between lower blood Pb levels (e.g., <10 μg/dL) and worse renal function (Staessen et al., 1992). Reverse causality attributes increased Pb dose to reduced Pb excretion as a consequence of renal insufficiency. The temporal relation between Pb dose and renal function decline is a critical factor in determining causality. This can be assessed in longitudinal observations of participants with mean blood Pb levels in this lower dose range. Two analyses of longitudinal data from the Normative Aging Study population have been published to date (Kim et al., 1996; Tsaih et al., 2004). Lead dose predicted subsequent decline in renal function over follow-up periods ranging from 3 to 6 years. This was observed even after adjustment for renal function at the beginning of the follow-up period. Longitudinal studies in patients with renal insufficiency have reported

similar findings. Both blood and EDTA-chelatable Pb levels at baseline were significantly associated with decline in estimated GFR over a 4 year follow-up period in 121 patients, even after adjustment for a wide range of covariates, including baseline renal function (Yu et al., 2004) (discussed in Section 6.4.4.3). The same was true in a larger study of 202 chronic renal insufficiency patients over a 2-year follow-up period (Lin et al., 2003). Notably, in both studies, EDTA-chelatable Pb levels were <600 μg/72 h in all participants, with means well below this traditional cut-point. The PheeCad study (the 1990-95 follow-up to the Cadmibel study) appears to have collected relevant data, but the Pb data were not reported in the publication (Hotz et al., 1999).

Biologically, reverse causality should be most prominent in populations with renal insufficiency for a prolonged period of time. However, Kim et al. (1996) observed that blood Pb was positively associated over the entire serum creatinine range, most of which was normal in this general population study and where a substantial decrease in Pb excretion was unlikely. Further, in reverse causality, urinary excretion of Pb should decrease as renal function declines. Urine Pb is not a commonly used Pb dose biomarker, so data from the lower Pb exposure studies are generally not available to assess this. However, higher urine Pb was associated with lower estimated creatinine clearance in Swedish women (Akesson, 2006). Finally, the positive impact of Pb chelation on renal function (discussed in Section 6.4.4.3) may provide evidence against reverse causality. However, the possibility of a direct beneficial effect of the chelating agent on renal function cannot be excluded as an explanatory factor (Gonick et al., 1996). In summary, several lines of evidence suggest that reverse causality is not likely to be a major explanatory factor accounting for observed associations between Pb dose and renal dysfunction.

Consistency of the Magnitude of Associations

Slopes of the associations between blood Pb and creatinine clearance in the general population studies that provide data relevant for such a comparison are shown in Figure 6-8. Since these studies generally had mean blood Pb levels less than 10 μg/dL, slopes of the reported relations were estimated at a blood Pb level of 5 μg/dL. Measured or estimated creatinine clearance data were used from those studies that reported relations for those outcomes. For studies that only reported data for serum creatinine, the slope at a blood Pb of 5 μg/dL was estimated and then the slope was converted to a creatinine clearance slope using the

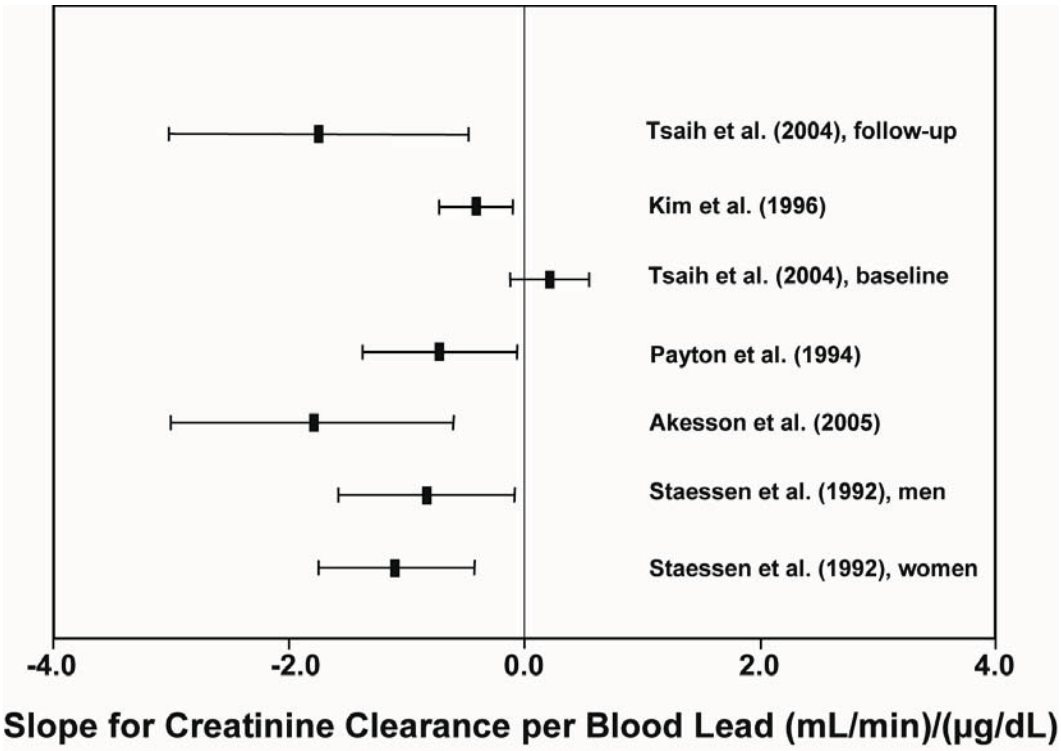

Figure 6-8. Creatinine clearance versus blood lead slope at a blood lead of 5 µg/dL.

Cockcroft-Gault equation (Cockcroft and Gault, 1976). Publication bias may impact the data available for this figure. No significant associations between blood Pb and renal function were observed in two of the general population studies; beta coefficients were not reported (Wu et al., 2003a; de Burbure et al., 2003). However, since Wu et al. (2003a) observed a significant association between patella Pb and creatinine clearance, the study is consistent with results in the majority of the other general population studies. Lastly, a third study (Pocock et al., 1984) reported only that the correlation coefficient between crude blood Pb and serum creatinine was 0.0. Furthermore, publications derived from evaluation of the Normative Aging Study population outnumber those from other populations. Slopes ranged from 0.2 to −1.8 mL/min change in creatinine clearance per µg/dL increase in blood Pb.

Clinical Relevance

It is now clear that chronic kidney disease (CKD) at earlier stages than those requiring actual renal dialysis or transplantation represents a risk factor for cardiac disease and other

causes of mortality and morbidity (Levey et al., 2003). The clinical relevance of the Pb effect can be estimated from the study by Akesson et al. (2005), in which the 5th and 95th percentile values for blood Pb were reported. An increase in blood Pb from the 5th to the 95th percentile (3.5 μg/dL) has the same adverse impact on glomerular filtration as an increase of 4.7 years in age or 7 kg/m^2 in body mass index, both of which are known renal risk factors. In populations at high risk for Pb exposure, a 10-fold increase in blood Pb (e.g., from 1 to 10 μg/dL) would result in an 16.2 mL/min decrease in estimated creatinine clearance or a 22.5% decrease from the mean (Akesson et al., 2005). Sixteen and 9% declines due to a 10-fold increase in blood Pb were predicted based on data for women (Staessen et al., 1992) and men (Payton et al., 1994), respectively. Although Pb exposure is higher in rapidly industrializing countries, high risk populations remain in the United States. In populations with lower blood Pb levels, a downward shift in renal function of the entire population due to Pb may not result in CKD in identifiable individuals; however, that segment of the population with the lowest renal reserve may be at increased risk for CKD when Pb is combined with another renal risk factor. The potential public health importance of population shifts is discussed by the American Thoracic Society (2000) and Rose and Day (1990). Data in both general and patient populations support this concept for Pb exposure. Of note, the above estimates are for general populations. Effect estimates for susceptible populations, such as those with diabetes, hypertension, or chronic renal insufficiency from non-Pb related causes, are likely to be higher.

At-risk Populations

Susceptible populations include those with other risk factors for renal disease, including hypertension, diabetes, and renal disease from other causes. Lead-exposed populations also at increased risk for obesity, diabetes, and hypertension represent groups likely to be the most impacted by Pb exposure. Frequently, both Pb and other risk factors are present in the same lower SES status groups.

In conclusion, the general population literature on the adverse renal effects of Pb benefits from a number of strengths. The consistent associations observed in the majority of these studies provide strong evidence indicating that Pb is a contributor to renal dysfunction in susceptible populations at much lower Pb exposure levels than those previously identified based on data available at the time of the 1986 Lead AQCD.

6.4.4.2 Occupational Studies

The vast majority of studies in the Pb-renal literature were conducted in the occupational setting. This was especially true prior to the 1986 Lead AQCD, but is still also currently the case. Occupational studies of the renal effects of Pb are presented in Annex Table AX6-4.2. In contrast to the general population research discussed above, research on the adverse renal effects of occupational Pb exposure is much less consistent. This is puzzling, since most dose-response relations are thought to be linear. Therefore, biologically, notably elevated Pb doses (as indexed by 30-50 μg/dL blood Pb levels) should be nephrotoxic if lower doses are. Several explanations for this seeming inconsistency are possible. Some are unique to the occupational literature, such as smaller sample sizes. In addition, employed workers are typically healthier and younger than the general population—resulting in the healthy worker bias. This is a particular problem as susceptible risk groups are identified. Survivor bias in cross-sectional studies is also a concern, since workers whose renal function has declined are generally removed from exposure, particularly if they are followed in a medical surveillance program. Few studies have included former workers. Also, statistical analyses have been more limited in occupational studies. Analyses for some outcomes were limited to comparisons between exposed workers and controls whose Pb levels were in the range associated with adverse renal outcomes in environmental work. Use of multiple linear regression has generally involved more limited adjustment for covariates than in most of the environmental studies. Many of these limitations result in bias towards the null, which increases the risk that true associations may not be detected.

Other limitations are pertinent for research on the adverse renal effects of Pb exposure in any population. These factors are likely to have a greater impact on the validity of studies in which one or more of the biases discussed above are also present. These include the insensitivity of the clinical renal outcomes and the lack of uniformly accepted early markers of renal damage in Pb exposure. Limited Pb exposure assessment may also be a factor. Finally, Pb appears to be able to induce an element of hyperfiltration in some settings. Hyperfiltration is a process initially observed in diabetes but is also implicated in other settings, including hypertension and obesity (Nenov et al., 2000). In this process, initial supranormal renal function is paradoxically associated with increased risk for subsequent renal dysfunction. Several occupational studies have reported statistically significant higher mean creatinine clearance in Pb-exposed workers

compared to controls and/or positive associations between higher Pb dose and lower BUN, serum creatinine and/or higher creatinine clearance (Roels et al., 1994; Weaver et al., 2003a, 2005a; Hsiao et al., 2001). Hu (1991) has also reported increased mean creatinine clearance in 22 adults who were Pb poisoned as children, as compared to matched controls (discussed in Section 6.4.5.1), and a recent study reported higher blood Pb to be associated with lower serum creatinine and cystatin C in a study of 800 European children (discussed in Section 6.4.5.3). Longitudinal data for Pb-exposed rodents (discussed in Section 5.7.4.2) are critical in relating this process to Pb. However, in that work, despite similar initial hyperfiltration, subsequent renal dysfunction was much more severe in the high-dose Pb-exposed rodents compared to the low-dose animals. This suggests that hyperfiltration may be one, but not the only, mechanism underlying adverse renal effects of Pb. Whether hyperfiltration contributes to pathology in humans is unclear; longitudinal studies are needed. Regardless, the issue for risk assessment is that significant findings could be obscured if opposite direction associations are present in different segments of the study population and interaction models are not performed to address this.

In the work of Weaver et al. (2003a), no associations were observed when the entire population was studied by several models; however, when interaction models using age as the effect modifier were evaluated, significant associations in opposite directions were observed. This is illustrated in Figure 6-9. This is a valid concern for risk assessment, since the factors involved in these inverse associations in Pb-exposed populations are not well defined at present. Weaver and colleagues have used age as the effect modifier; however, other factors, such as Pb job duration, may be important as well.

In conclusion, a number of limiting factors are observed in the body of research on occupational Pb exposure and adverse renal outcomes. Most of these factors increase the risk that true associations will be missed (bias towards the null). Moreover, Pb appears to have a paradoxical effect on the kidney that further increases this possibility. As a result, the more consistent body of literature in general populations at current Pb exposure conditions provide an appropriate data base for assessing potential renal effects.

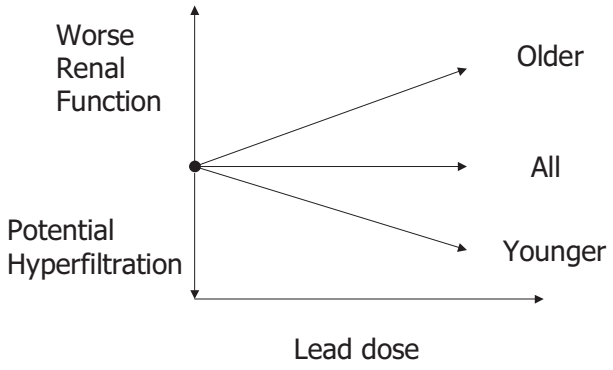

Figure 6-9. Effect on associations between lead dose and renal function depending on whether effect modification (age in this example) is assessed.

6.4.4.3 Patient Population Studies

Studies in various patient populations have also contributed to the body of knowledge concerning adverse renal impacts of Pb exposure (summarized in Annex Table AX6-4.3). Populations studied include those with chronic renal insufficiency (CRI), end-stage renal disease (ESRD), gout, and hypertension, since these diseases are thought to be increased by high-level Pb exposure, particularly when two or more coexist in the same patient. Early research focused on patients with potential Pb nephropathy; and Pb body burdens of interest, assessed with EDTA chelation, were above 600 to 650 μg/72 h. These studies suggested that chelation might be beneficial in Pb nephropathy (Morgan, 1975; Wedeen et al., 1979).

Recurring concerns in this work are, first, whether Pb body burden is higher in all patients with renal insufficiency or failure due to decreased Pb excretion (reverse causality); and, second, whether EDTA-chelatable Pb levels, when measured over a 72-h period in patients with CRI, can be equated to those in participants with normal renal function measured over 24 h. It is possible that, due to decreased excretion of EDTA in renal insufficiency, more Pb per dose is ultimately chelated.

Chelation also may have a direct beneficial effect on kidney function, regardless of Pb exposure, since DMSA has been reported to prevent renal damage in a non-Pb-exposed rat model of nephrosclerosis (Gonick et al., 1996). If so, the benefits of chelation do not appear to

occur via reversal of structural damage (Khalil-Manesh et al., 1992); improved hemodynamics from reduction of reactive oxidant species may be a mechanism (Gonick et al., 1996).

In one of the key studies, Yu et al. (2004) followed 121 patients over a 4-year period. Eligibility required well-controlled CRI. Importantly, serum creatinine between 1.5 and 3.9 mg/dL and EDTA-chelatable Pb <600 µg/72 h were required at baseline. Patients with potentially unstable renal disease were excluded (i.e., due to systemic diseases such as diabetes). Mean age of the study population was 57 years. Mean blood Pb and EDTA-chelatable Pb levels were 4.2 µg/dL and 99.1 µg/72 h, respectively. In a Cox multivariate regression analysis, chelatable Pb was significantly associated with overall risk for the primary endpoint (doubling of serum creatinine over the 4-year study period or need for hemodialysis). The hazard ratio for each 1 µg chelatable Pb was 1.01 (95% CI: 1.00, 1.01; p = 0.002). Of the many traditional renal risk factors adjusted for in these models, only the diagnosis of chronic interstitial nephritis was significantly associated with an increase in GFR. Associations between baseline chelatable Pb or blood Pb level and change in GFR (estimated by an MDRD equation [Levey et al., 1999]) were modeled separately using GEE. Based on these models, a 10 µg higher chelatable Pb level or 1 µg/dL higher blood Pb level reduced the GFR by 1.3 and 4.0 mL/min, respectively, during the 4-year study period. This work supports results observed for general populations by suggesting that Pb is nephrotoxic in susceptible populations at lower levels than currently appreciated.

6.4.4.4 Mortality Studies

As summarized in Steenland et al. (1992), mortality studies have consistently shown excess mortality from chronic kidney disease in Pb workers. This increased risk has been most apparent in workers exposed in earlier time periods, becoming nonsignificant in later calendar time periods in a number of studies. Steenland et al. (1992) reported similar results in a study of 1990 former Pb smelter workers. This cohort was made up of predominantly White men who had worked in a Pb-exposed department for at least 1 year between 1940 and 1965. Mean (SD) blood Pb, measured in 1976 in 173 members of this cohort, was 56.3 µg/dL (12.9). There were 8 deaths from chronic kidney disease. Compared to the U.S. White male population, the standardized mortality ratio was 1.26 (95% CI: 0.54, 2.49). The standardized mortality ratio increased with duration of exposure from 0.79 in Pb workers exposed 1 to 5 years to 2.79 in workers exposed for >20 years, although the standardized mortality ratios did not reach

statustical significance (CI not reported). Lead exposure in U.S. industries has declined over the years, and this has been hypothesized as an explanation for the reduction in mortality from renal disease observed in this type of study. However, that fact that improved treatments for chronic renal disease have led to a decrease in mortality from end-stage renal disease (U.S. Renal Data System, 2004) may also be an important factor. The mortality studies by Steenland et al. (1992) and others are described further in Annex Table AX6-4.4.

6.4.5 Lead Nephrotoxicity in Children

6.4.5.1 Studies in Adults Following Childhood Lead Poisoning

Henderson clearly established an increased risk for Pb nephropathy in adult survivors of untreated childhood Pb poisoning (Henderson, 1955). Lead nephropathy was responsible for substantial mortality in the Queensland, Australia population. However, as noted in the 1986 Lead AQCD, other studies of adults who survived childhood Pb poisoning have not reported this degree of renal pathology. Studies published since 1986 are presented in Annex Table AX6-4.5 and also have not observed the degree of renal pathology noted in the Queensland work. Chelation when Pb poisoning was diagnosed may be an explanatory factor in some of these studies.

A study comparing 21 adults, who had experienced childhood Pb poisoning between 1930 and 1942, to age-, sex-, race-, and neighborhood-matched controls found no significant differences in blood Pb level, serum creatinine, or BUN (Hu, 1991). Mean measured creatinine clearance was unexpectedly higher in the previously Pb-poisoned group compared to controls (112.8 versus 88.8 mL/min/1.73 m^2 [$p < 0.01$]). The mean in the Pb-exposed group was also higher than the predicted value of 94.2 mL/min/1.73 m^2 from the nomogram of Rowe et al. (1976). One survivor, who was identified but not included in the study, had been diagnosed with chronic interstitial nephritis on renal biopsy. Her blood Pb was 30 μg/dL, and her presentation was thus consistent with actual Pb nephropathy. Strengths of this study included clear criteria for Pb poisoning and assessment of clinical renal function that included both measured and estimated creatinine clearances. However, the study was limited by small size and the fact that the number enrolled was a very small subset of the initially identified cohort of 192. At least 43 (22.4%) of the 192 were confirmed to be deceased. That group had evidence of higher initial Pb exposure, which raises concern regarding survivor bias in the study group. More importantly,

the higher mean creatinine clearance in the Pb-exposed group provides further evidence for Pb-related hyperfiltration. Again, as discussed in the occupational study section, this may hamper attempts to detect associations between Pb dose and adverse renal effects.

6.4.5.2 Lead Body Burden in Children with Chronic Renal Disease

Schärer et al. (1991) reported higher Pb content in deciduous teeth in 22 German children, age 5 to 14 years, with varying degrees of renal insufficiency compared to a control group of 20 siblings or neighbors and a group of 16 children without known Pb exposure. Mean dental Pb content was 2.8, 1.7, and 1.4 μg/g, in the three groups, respectively. Lead levels in teeth were significantly higher in both the patient and sibling/neighbor control groups compared to the unexposed control group. Mean blood Pb in the renal patients was only 2.9 μg/dL (range 1.1-10.1 μg/dL). Lead in teeth was not correlated with duration of renal impairment. The authors attributed elevated Pb levels to both exposure and accumulation from decreased renal excretion.

6.4.5.3 Environmental Studies in Children

The insensitivity of the clinical renal outcome measures for early renal damage is a particular problem in children who do not have many of the other renal risk factors, such as hypertension and diabetes, that older adults do. As a result, recent studies in children have favored early biological effect (EBE) markers over clinical renal measures. However, data to determine the predictive value of such biomarkers for subsequent renal function decline in Pb exposed populations are extremely limited. Coratelli et al. (1988) reported a decline in urinary NAG in association with a 1 month period of decreased occupational exposure in 20 adult Pb battery factory workers followed over a 1 year period. Clinical renal function measures were not studied however. Sarasua et al. (2003) studied 526 adults and children, a mean of 4.5 years after an initial evaluation of renal function including measurement of urinary albumin, NAG, RBP, and alanine aminopeptidase. These participants were drawn from three populations exposed to volatile organic compounds and explosives via groundwater and controls. Follow-up was performed to determine if the EBE markers remained elevated and whether the presence of elevated EBE markers at baseline was associated with abnormalities in serum creatinine, serum cystatin C, 24 h creatinine clearance, and urine osmolality at follow-up. Among children who

had elevated EBE markers at baseline, renal EBE markers remained elevated in 38%. However, none remained elevated in the 32 who had completed adolescence by the time of the follow-up. The authors noted the potential for puberty related biomarker changes. Also, abnormalities in the clinical measures were rare at follow-up.

The environmental studies in children generally focused on children living near industrial sources and controls. These studies are summarized in Annex Table AX6-4.5. Three studies that included analysis of clinical renal outcomes are of note. Fels et al. (1998) found no difference in mean serum creatinine between 62 exposed and 50 control children; correlations, if assessed were not reported. Staessen et al. (2001) studied 200 17-year-old Belgian children. The two exposed groups were recruited from industrialized suburbs, whereas the control group was recruited from a rural area. Mean blood Pb levels were 1.5, 1.8, and 2.7 μg/dL in controls, and exposed groups one and two, respectively. Although blood Pb levels were low, after adjustment for sex and smoking status, blood Pb was positively associated with both serum cystatin-C and urinary β_2-microglobulin. Blood Cd was not associated with either outcome. In contrast, De Burbure et al. (2006) observed associations between higher blood Pb and lower serum creatinine and cystatin C in models with 300-600 European children (depending on outcome). The authors considered this to be suggestive of hyperfiltration. Additional research in children, including longitudinal follow-up, is needed.

6.4.6 Mechanisms for Lead Nephrotoxicity

Individuals who have been heavily exposed to Pb are at increased risk for both gout and renal disease (Shadick et al. 2000; Batuman 1993). Lead is thought to increase serum uric acid (urate) by decreasing its renal excretion (Emmerson, 1965; Ball and Sorensen, 1969; Emmerson and Ravenscroft, 1975). As discussed above, research during the past decade indicates that Pb is nephrotoxic at lower levels than previously recognized. The same is true for uric acid (Johnson et al., 2003). Therefore, it is possible that one mechanism for Pb-related nephrotoxicity, even at current lower levels of Pb exposure, is via increasing serum uric acid.

In order to address this question, Weaver et al. (2005a) analyzed data from 803 current and former Pb workers to determine whether Pb dose was associated with uric acid and whether previously reported associations between Pb dose and renal outcomes (Weaver et al., 2003a) were altered after adjustment for uric acid. Outcomes included uric acid, blood urea nitrogen,

serum creatinine, measured and calculated creatinine clearances, and urinary NAG and RBP. Mean uric acid, tibia Pb, and blood Pb levels were 4.8 mg/dL (SD 1.2), 37.2 μg/g bone mineral (SD 40.4), and 32.0 μg/dL (SD 15.0), respectively. None of the Pb measures (tibia, blood, and DMSA-chelatable Pb) were associated with uric acid, after adjustment for age, gender, body mass index, and alcohol use. However, when effect modification by age on these relations was examined, both blood and tibia Pb were significantly associated in participants in the oldest age tertile ($\beta = 0.0111$ [95% CI: 0.003, 0.019] and $\beta = 0.0036$ [95% CI: 0.0001, 0.007]) for blood and tibia Pb, respectively). These models were further adjusted for blood pressure and renal function. Hypertension and renal dysfunction are known to increase uric acid. However, they are also risks associated with Pb exposure. Therefore, adjustment for these variables in models of associations between Pb dose and uric acid likely results in overcontrol. On the other hand, since non-Pb-related factors contribute to both renal dysfunction and elevated blood pressure, lack of adjustment likely results in residual confounding. Therefore, as expected, associations between Pb dose and uric acid decreased after adjustment for systolic blood pressure and serum creatinine, although blood Pb remained borderline significantly associated ($\beta = 0.0071$ [95% CI: −0.001, 0.015]). However, when the population was restricted to the oldest tertile of workers with serum creatinine greater than the median (0.86 mg/dL), likely the highest risk segment of the population, blood Pb remained significantly associated with uric acid even after adjustment for systolic blood pressure and serum creatinine ($\beta = 0.0156$). Next, in models of renal function in all workers, uric acid was significantly associated with all renal outcomes except NAG. Finally, in the oldest tertile of workers, after adjustment for uric acid, associations between Pb dose and NAG were unchanged, but fewer of the previously significant ($p \leq 0.05$) associations noted between Pb dose and the clinical renal outcomes in Weaver et al. (2003a) remained significant.

Data from the Normative Aging Study indicate that Pb dose, at levels lower than those known to increase the risk for gout or in the study of Weaver et al. (2005a), is associated with increased uric acid (Shadick et al., 2000). In 777 participants, mean blood, patella, and tibia Pb levels were 5.9 μg/dL, 30.2 μg/g bone mineral, and 20.8 μg/g bone mineral, respectively. A significant association between patella Pb and uric acid ($\beta = 0.007$ [95% CI: 0.001, 0.013]; $p = 0.02$) was found, after adjustment for age, BMI, diastolic blood pressure, alcohol ingestion, and serum creatinine. Borderline significant associations between tibia ($p = 0.06$) and blood

Pb ($p = 0.1$) and uric acid were also observed. Notably these associations were significant even after adjustment for blood pressure and renal function, providing further evidence that low-level Pb exposure increases uric acid.

These data suggest that older workers comprise a susceptible population for increased uric acid due to occupational Pb exposure. Uric acid may be one mechanism for Pb-related nephrotoxicity. However, this is not the only mechanism, since in Weaver et al. (2005a), the association between blood Pb and serum creatinine remained significant even after adjustment for uric acid. These mechanistic relations have more than just theoretical importance. Clinically relevant therapies may be possible since EDTA chelation has been reported to improve both renal function and urate clearance in patients with renal insufficiency and gout, even when EDTA-chelatable Pb body burdens were low (Lin et al., 2001b).

6.4.7 Susceptible Populations for Lead Nephrotoxicity

6.4.7.1 Chronic Medical Diseases

The general population studies by Tsaih et al. (2004) and Muntner et al. (2003) (discussed in Section 6.4.4.1) indicate that patient populations with diabetes and hypertension are at increased risk for adverse renal effects of Pb. Lin et al. (2001a, 2002) indicate that patients with CRI and gout are also at increased risk. In these settings, Pb appears to acts as a cofactor with other renal risk factors to cause early onset of renal insufficiency and/or a steeper rate of renal function decline. It is likely that the presence of larger high risk populations within general populations is an important factor in the lower Pb dose thresholds noted for the adverse effects of Pb on the kidney in environmental compared to occupational research.

6.4.7.2 Age

Weaver et al. (2003a, 2005a,b) found older age to be a risk factor for adverse renal effects in Korean Pb workers. This is consistent with research in general populations (Lindeman et al., 1985) and is biologically plausible, since most renal risk factors increase with age. Gonick and Behari (2002) have summarized the data regarding the potential contribution of Pb exposure to essential hypertension; similar issues may be involved with the renal dysfunction observed in aging.

6.4.7.3 Genetic Polymorphisms

Research in the last two decades suggests that several genetic polymorphisms affect Pb toxicokinetics (i.e., modify the relation between Pb exposure and dose). Of those potentially relevant to the kidney, data on the gene that encodes for ALAD are the most important in this regard. The ALAD enzyme is a principal Pb-binding protein; the isozymes in those with the ALAD2 allele are more electronegative and bind a greater proportion of blood Pb than does the protein in individuals with the ALAD 1-1 genotype (Bergdahl et al., 1997). Research to date indicates that individuals with the ALAD2 allele generally have higher blood Pb levels than those with the ALAD 1-1 genotype, although this may not be the case at lower levels of Pb exposure (i.e., mean blood Pb levels <10 μg/dL) (Kelada et al., 2001). Participants with the ALAD2 allele have been found to have lower bone Pb levels in some studies (Hu et al., 2001; Kamel et al., 2003); other toxicokinetic differences have also been reported (Fleming et al., 1998; Hu et al., 2001; Schwartz et al., 1997; Smith et al., 1995). Overall, these data suggest that tighter binding of Pb by the isozymes of the ALAD2 allele decreases Pb sequestration in bone.

In contrast, data to determine whether the ALAD polymorphism impacts the renal toxicity of Pb are still quite limited. The only environmentally exposed population in which this has been addressed is the Normative Aging Study. Wu et al. (2003a) (discussed in detail in Section 6.4.4.1.2) analyzed data to determine whether the ALAD genetic polymorphism modified associations between Pb dose and uric acid, serum creatinine, and estimated creatinine clearance. A total of 114 (16%) of the study group were either homozygous or heterozygous for the variant ALAD2 allele. None of the three outcomes were significantly different by genotype. However, effect modification by genotype on the association between tibia Pb and serum creatinine was observed; the β coefficient (and slope) was greater in the group with the variant allele ($\beta = 0.002$ [SE not provided]; $p = 0.03$). Effect modification of borderline significance ($p < 0.1$) for relationships between patella or tibia Pb and uric acid was observed; this was significant in participants whose patella Pb levels were above 15 μg/g bone mineral ($\beta = 0.016$ [SE not provided]; $p = 0.04$). Similar to the serum creatinine model, patella Pb was associated with higher uric acid in those with the variant allele. Genotype did not modify Pb associations in models of estimated creatinine clearance.

The impact of the ALAD polymorphism on renal outcomes has been studied in four occupationally-exposed populations to date. The two that assessed both associations and effect

modification by genotype are discussed here. Weaver et al. (2003b) analyzed data from 798 Pb workers. A total of 79 (9.9%) participants were heterozygous for the ALAD2 allele (none was homozygous). After adjustment, participants with the ALAD2 allele had lower mean serum creatinine and higher calculated creatinine clearance. Effect modification by ALAD on associations between blood Pb and/or DMSA-chelatable Pb and three of six renal outcomes was observed. Among those with the ALAD 1-2 genotype, higher Pb measures were associated with lower BUN and serum creatinine and higher calculated creatinine clearance. Among older workers (age ≥ median of 40.6 years), ALAD genotype modified associations between Pb dose and uric acid levels. Higher Pb dose was significantly associated with higher uric acid in workers with the ALAD 1-1 genotype; associations were in the opposite direction in participants with the variant ALAD 1-2 genotype (Weaver et al., 2005c).

Ye and colleagues (2003) assessed effect modification by ALAD on associations between blood Pb with urinary NAG and albumin in a study of 216 Pb workers. Geometric mean blood Pb was 37.8 µg/dL in 14 workers with the ALAD 1-2 genotype and 32.4 µg/dL in workers with the ALAD 1-1 genotype. After adjustment for age, NAG was borderline statistically higher in those with the variant allele whose blood Pb levels were ≥40 µg/dL. In all Pb workers, after adjustment for age, gender, smoking, and alcohol ingestion, a statistically significant positive association between blood Pb and creatinine adjusted NAG was observed in the workers with the ALAD 1-2 genotype but not in Pb workers with the ALAD 1-1 genotype (the groups were analyzed separately rather than in an interaction model).

Thus, two of the three studies reported steeper slopes for one or more associations between Pb dose and adverse renal function in participants with the ALAD2 allele compared to those with the ALAD 1-1 genotype, which suggests that the variant ALAD gene confers additional risk for adverse renal outcomes in Pb-exposed populations. If the associations of Weaver et al., (2003b) represent Pb-induced hyperfiltration, their results could be consistent with increased risk from the variant allele as well. Ultimately, analysis of longitudinal data in the Korean Pb worker population will be needed to understand these complex relationships.

6.4.8 Confounding of the Renal Effects of Lead by Other Potential Risk Factors

Studies selected for discussion in Section 6.4 above have generally controlled for at least the most basic risk factors known to affect renal function, such as age, gender, and body mass index (or weight and height separately). Some have controlled for many other potentially important risk factors. In addition, exposure to other nephrotoxicants must be considered. Notably, although these are listed under confounders, some may be effect modifiers as well.

6.4.8.1 Cadmium

Similar to Pb, cadmium (Cd) is an ubiquitous nephrotoxicant that accumulates in the body. Environmental exposure to Cd in the United States occurs primarily through food and smoking (Agency for Toxic Substances and Disease Registry, 1993). Cadmium in food is a result of soil pollution from a variety of human activities such as phosphate fertilizer use, industrial releases from smelting, and fuel combustion. An analysis of NHANES III data, collected in a representative sample of the U.S. population from 1988-1994, indicates that mean urinary Cd is 0.48 μg/g creatinine, and 97.7% of the population has a level ≤2.0 μg/g creatinine (Paschal et al., 2000). Also similar to Pb, Cd causes proximal tubule pathology and is a known risk factor for chronic renal insufficiency (CRI).

Existing data indicate that Cd, at exposure levels common in the United States, confounds associations between Pb exposure and at least one renal outcome, NAG. Roels et al. (1994) reported higher mean NAG in their Pb-exposed group; however, NAG was correlated with urinary Cd but not blood or tibia Pb, despite mean urinary Cd being only 1.04 and 0.53 μg/g creatinine in workers and controls, respectively. Cardenas et al. (1993) reported a similar finding. Bernard et al. (1995a) found an association between urinary Cd and the NAG-B isoenzyme (released with breakdown of proximal tubular cells) in 49 Cd workers and 20 age-matched controls. In multiple linear regression, urinary Cd, but not Pb, was associated with NAG-B after adjustment for age. The association was significant even in the 44 participants with Cd levels <2 μg/g creatinine. However, NAG-A (released by exocytosis) was correlated with urinary Pb (the only Pb measure), but not Cd. Roels et al. (1995) reviewed data pertinent to the potential for Cd confounding of associations between Pb and NAG. In more recent work, Weaver et al. (2003a) measured urinary Cd in a subset of 191 of the 803 workers in their study

(mean urinary Cd was 1.1 μg/g creatinine). Higher urinary Cd levels were associated with higher NAG. Of the Pb measures obtained, only tibia Pb was significantly associated with NAG in the Cd subset. When urinary Cd and tibia Pb were entered as covariates in the same model, both remained associated with NAG ($p < 0.05$). However, in comparing the effects, a 0.5 μg/g creatinine increase in Cd had the same effect on NAG as a 66.9 μg/g bone mineral increase in tibia Pb. When compared by ranges of exposure in this population, environmental level Cd dose had a larger impact on NAG than did occupational Pb dose.

Cadmium exposure may well confound relations between Pb exposure and other renal outcomes as well, but available data are too limited to draw firm conclusions. Positive associations between urinary Cd, which is thought to be the best measure of cumulative Cd exposure in the absence of Cd-related renal damage, and low molecular weight (LMW) proteinuria are well established in the occupational setting. LMW proteinuria, most commonly assessed by β_2-microglobulin, is generally progressive at Cd levels >1500 μg/g creatinine in workers with substantial body burdens (one or more historical urinary Cd >20 μg/g creatinine) but may also be progressive at lower levels (Roels et al., 1997; Bernard, 2004). More importantly, clinical renal function also declines as evidenced by decreasing GFR in Cd-exposed workers followed longitudinally after removal from exposure due to LMW proteinuria (Roels et al., 1989; 1997).

In contrast to the clear evidence that Cd is a renal toxicant at occupational levels of exposure, the renal risk from lower level Cd exposure remains uncertain. Most studies of environmental Cd exposure are cross-sectional and have assessed EBE markers, rather than clinical renal outcomes (Alfvén et al., 2002; Järup et al., 2000; Noonan et al., 2002; Olsson et al., 2002). The Cadmibel study, a general population study of exposed residents from both Cd-polluted and unpolluted areas (discussed in Section 6.4.4.1.1), found correlations between urinary Cd and several urinary EBE markers (NAG, RBP, β_2-microglobulin, calcium, and amino acids) (Buchet et al., 1990). In those models, after adjustment for urinary Cd and other covariates, blood Pb was significant in models of β_2-microglobulin and amino acids but not NAG. However, in this same population, blood Pb was inversely associated with creatinine clearance, whereas urinary and blood Cd were not (Staessen et al., 1992). A 5-year follow-up was conducted to determine the significance of the EBE abnormalities (Hotz et al., 1999). In this study, models of renal function (two dichotomized outcomes: a 20% decline in creatinine

clearance and a 20% increase in albumin excretion) in relation to quartiles of urinary Cd and the EBE markers at baseline were analyzed by likelihood ratios. Baseline variables did not predict adverse renal outcomes. However, 25% of the original population was lost to follow-up; available data indicated that their baseline renal function was worse than those who participated in the follow-up study. This may have biased the study towards the null.

Three recent publications suggest that low-level Cd exposure is associated with adverse clinical renal outcomes. Elevated urine Cd levels were associated with decreased calculated creatinine clearance and with prevalent microalbuminuria after adjustment for age, sex, race, smoking, and use of diuretics in an analysis of 16,094 participants in the NHANES III study (Young et al., 2004). Also, Hellström et al. (2001) reported increased rates of renal dialysis and transplantation in residents of Cd-polluted areas in Sweden. Compared to the "no exposure group" (domicile >10 km from a battery plant), age-standardized rate ratios were 1.4 (95% CI: 0.8, 2.0) in the low-exposure group (domicile 2 to 10 km) and 1.9 (95% CI: 1.3, 2.5) in the moderate-exposure group (domicile <2 km). Exposure categorization was based on environmental monitoring in the study areas. Cadmium dose was not directly measured, although occupationally exposed participants were considered in a separate group. The third study, by Åkesson et al. (2005), also assessed Pb exposure as a covariate, an important approach given the Cadmibel results (Staessen et al., 1992). Blood and urinary Cd were associated with worse GFR and creatinine clearance. The association for blood Cd and decreased creatinine clearance remained statistically significant even in non-smokers, suggesting that a public health remedy, in addition to smoking cessation, may be of value.

In conclusion, Cd clearly confounds associations between Pb dose and NAG. Given the similarities in both nephrotoxicants, Cd may confound and/or modify associations between Pb and other renal outcomes. However, data regarding the concentration-response relationship between environmental Cd and the kidney are too limited to assess the potential for this at present. Future studies assessing both Pb and Cd are needed.

6.4.9 Summary of the Epidemiologic Evidence for the Renal Effects of Lead

During the past two decades, the quality of research on the renal impacts of Pb exposure has advanced dramatically. As a result, a much more accurate assessment of the adverse renal impact of Pb exposure can now be made. General population studies are the most important

advance in this regard. These studies provide strong evidence that renal effects occur at much lower blood Pb levels than previously recognized. These effects are clinically relevant in U.S. subpopulations who continue to have higher Pb exposure than the general population. At levels of exposure in the general U.S. population overall, Pb combined with other risk factors, such as diabetes, hypertension, or chronic renal insufficiency from non-Pb related causes, can result in clinically relevant effects. Notably, the size of such susceptible populations is increasing in the United States due to obesity.

- The majority of studies in general adult and patient populations published during the past two decades have observed associations between Pb dose and worse renal function. Other explanations, such as residual confounding or reverse causality, are less likely. The renal effects of Pb on children are difficult to assess, as most of these studies only measured early biological effect markers which have unknown clinical significance.

- The magnitude of the effect of Pb on renal function ranged from 0.2 to –1.8 mL/min change in creatinine clearance per μg/dL increase in blood Pb in general population studies. The size of the effect was relatively consistent across the studies, although only five provided data useful for this determination (three were at different time points in the Normative Aging Study population) and a form of publication bias may be present in studies that provided no data and only reported that associations were not significant. One patient population (individuals with CRI) study reported a similar effect of blood Pb longitudinally on yearly decline in GFR.

- The cumulative effect of higher blood Pb levels from past exposure may be a factor in nephrotoxicity observed at current blood Pb levels. However, one study found associations between blood Pb and concurrent serum creatinine in participants whose peak blood Pb levels were $\leq$10 μg/dL.

- The threshold for Pb-related nephrotoxicity cannot be determined based on current data. However, associations with clinically relevant renal outcomes have been observed in populations with mean blood Pb levels as low as 2.2 μg/dL.

- Research in the occupational setting is far less consistent. However, a notable finding from several of these studies is the observation of inverse associations (higher Pb dose with lower BUN, serum creatinine, and/or higher creatinine clearance). This may indicate Pb-related hyperfiltration and may have mechanistic implications.