NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDIX D:
HUMAN STUDIES OF RENAL EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Akesson (2005) Sweden	816 Swedish women from the Women's Health in the Lund Area (WHILA), 726 with blood Pb available; Year= 1999-2000 Male = 0%	Median (5-95% percentiles): 58 (53-64)	Median (5-95% percentiles): 2.2 (1.1-4.6)	GFR (based on cystatin C); creatinine clearance; α1-microglobulin; NAG *Primary exposure assessed in study was Cd*	Multiple linear regression; Age, BMI, diabetes, hypertension, and regular use of nephrotoxic drug, blood and urinary Cd (in separate models), smoking status by stratification	<u>Multiple logistic regression with blood Pb, β (95%CI):</u> **GFR (mL/min; adjusted for urinary Cd)** **All (n=816): -0.20 (-0.32 to -0.09)** **Never-smokers: -0.26 (-0.43 to -0.09)** **GFR (mL/min; adjusted for blood Cd)** **All (n=816): -0.20 (-0.30 to -0.07)** **Never-smokers: -0.20 (-0.4 to -0.07); significant interaction with diabetes** **creatinine clearance (mL/min; adjusted for urinary Cd)** **All (n=816): -0.18 (-0.30 to -0.06)** **Never-smokers: -0.30 (-0.5 to -0.1)** **creatinine clearance (mL/min; adjusted for blood Cd)** **All (n=816): -0.18(-0.30 to -0.07)** **Never-smokers: -0.30 (-0.5 to -0.1)** urinary α1-microglobulin (µg/L; adjusted for urinary Cd) All (n=816); NS (data not reported) Never-smokers: NS (data not reported) urinary α1-microglobulin (µg/L; adjusted for blood Cd) All (n=816); NS (data not reported) Never-smokers: NS (data not reported) urinary NAG (U/L; adjusted for urinary Cd) All (n=816): NS (data not reported) Never-smokers: NS (data not reported) urinary NAG (U/L; adjusted for blood Cd) All (n=816): NS (data not reported) Never-smokers: NS (data not reported)	Blood Pb is negatively correlated with GFR and creatinine clearance, but not α1-microglobulin and NAG.
Cross-sectional Alfven (2002) Sweden	1,021 individuals living near two battery plants (479 men, 542 women); 117 participants were current or former workers from plants. Part of the OSCAR (osteoporosis-cadmium as a risk factor study Year not stated Male = 47%	Men = 54 (10^{th} and 90^{th} percentiles: 18-81) Women = 52 (10^{th} and 90^{th} percentiles: 16-81)	male: 3.3 µg/dL female: 2.3 µg/dL	Urinary α_1-microglobulin	Multiple linear regression Age, smoking status, blood cadmium	men: 0.015 (-0.80 to 0.83) women: -0.19 (-0.99 to 0.60)	No association between blood Pb and urinary α_1- microglobulin
Cross-sectional Bernard (1995) Czech Republic	195 children aged 12-15 years referent area (n=51), "polluted" area 1 (n=91), "polluted"	12-15	Referent site: male: 8.7 µg/dL female: 8.39µg/dL Area 1:	β_2-microglobulin; urine RBP, Clara cell protein, urinary NAG activity, albumin	ANOVA on log-transformed data; Scheffe's multiple comparison test RBP and blood Pb	<u>Polluted areas relative to referents:</u> **β_2-microglobulin: ↑ area 1 (89.1 vs 60.3 µg/g creatinine); p<0.05** **Clara cell protein: ↑ area 1 (1.18 vs 0.62 µg/g creatinine); p<0.05**	↑ RBP in two polluted areas; increases in β_2-microglobulin, Clara cell

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	area 2 (n=53); Year not stated % male not stated		male:10.9 µg/dL female: 9.44 µg/dL Area 2: male: 14.9 µg/dL female: 12.9 µg/dL		multivariate analysis adjusted for age, sex, and other metals	**RBP: ↑ area 1 (109.4 vs 73.8 µg/g creatinine), ↑ area 2 (117.8 vs 73.8 µg/g creatinine); both p<0.05** **NAG: ↑ area 1 (2.32 vs 1.56 UI/g creatinine); p<0.05** Albumin: no differences <u>Continuous variable analysis:</u> RBP: significant correlation between urinary excretion and blood Pb (partial r^2=0.046, regression coefficient=0.302, p=0.005)	protein, and NAG were only noted in the "polluted" area with lower blood Pb levels. Albumin was not different in either area. Significant correlation between urinary excretion of RBP and blood Pb
Cross-sectional de Burbure (2003) France	600 adults living near two nonferrous smelters for ≥8 years compared to age (n=399) and gender-matched referents living in neighboring municipalities with unpolluted soil; Year not stated Male = 50%	Men: Polluted area= 34.6 (8.9) Referent = 35.2 (9.2) Women: Polluted area= 35.9 (9.6) Referent= 34.9 (8.6)	Polluted Area = male:6.8 (range: 1-24) female: 5.3 (range: 0.6-19) Referents = male: 7.1 (range: 1.1-26.2) female:4.2 (range: 0.2-15.4)	serum creatinine, urinary total protein, albumin, transferrin, β2-microblobulin, RBP, brush border antigen, NAG *Study assessed exposure to Pb, Cd, and Hg*	Multiple linear regression, t-test, and ANOVA Age, sex, BMI, area of residence, log urine Hg, log blood Cd and urinary creatinine	No statistically significant difference in any renal parameters (geometric means) in adults living in referent area (n= 86-91 men; 78-82 women) and "polluted" area (n= 147-155 men; 156-169 women) No significant correlations in multiple regression model (data not shown) Selected renal findings: Serum creatinine (mg/L) male: 14.3 (referent) vs 13.8 (polluted) female: 13.3 (referent) vs 12.6 (polluted) β2 microglobulin (µg/g creatinine) male: 68.16 (referent) vs 76.29 (polluted) female: 63.79 (referent) vs 71.98 (polluted)	No difference in renal parameters was observed, however blood Pb was higher in men from the "unpolluted" referent region compared to the "polluted" region
Cross-sectional de Burbure (2003) France *Population may overlap with de Burbure (2006)*	400 children living near two nonferrous smelters for ≥8 years compared to age and gender-matched referents living in neighboring municipalities with unpolluted soil; exclusionary criteria; obesity, diabetes and puberty; Year not stated Male = 50%	Range: 8.5-12.3	Exposed = male:4.2 (range: 0.5-14.8) female:3.7 (range: 0.8-16.6) Referents = male: 3.4 (range: 0.2-10.7) female: 2.7 (range: 0.2-12.6)	Urinary total protein, albumin, transferrin, β2-microblobulin, RBP, brush border antigen, NAG *Study assessed exposure to Pb, Cd, and Hg*	Multiple linear regression, t-test, and ANOVA Age, sex, BMI, area of residence, log urine Hg, log blood Cd and urinary creatinine	No significant correlations in multiple regression model Selected renal findings: β2 microglobulin (µg/g creatinine) male: 87.8 (referent) vs. 97.3 (polluted) female: 88.2 (referent) vs. 94.8 (polluted area)	No significant correlations between blood Pb and renal markers

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional de Burbure (2006) France, Czech Republic, and Poland *Population may overlap with de Burbure (2003)*	804 children from 3 countries living near two nonferrous smelters for ≥8 years compared to age and gender-matched referents living in neighboring municipalities with unpolluted soil in the same region of each country. Year not stated Male = 49.3%	8-5-12.3	382 French children: Exposed male(n=100): 4.2 (0.2) Referent male(n=94): 3.4 (0.2) Exposed female(n=94): 3.6 (0.2) Referent female (n=94): 2.8 (0.2) 174 Polish children: Exposed male (n=42): 6.5 (0.2) Referent male(n=35): 3.8 (0.1)- Exposed female(n=47): 5.7 (0.2) Referent female (n=50): 3.4 (0.1) 160 Czech children: Exposed male (n=42): 5.0 (0.1) Referent male(n=43): 3.6 (0.1) Exposed female(n=39): 4.1 (0.2) Referent female (n=36): 3.4 (0.1)	Serum creatinine, serum cystatin C, serum β2-microglogulin *Study assessed exposure to Pb, Cd, Hg, and As*	Step-wise multiple regression using logPb (blood), rank Cd (blood), rank Hg (urine), and log As (urine), log creatinine (urine), log BMI, age, sex, and area of residence Standardizations Serum Creatinine (1): creatinine (urine), sex, rank Cd (blood) x rank Hg (urine), and Pb (blood) x rank Hg (urine) Serum Creatinine (2): Cd (urine), creatinine (urine), sex, and Pb (blood) x rank Hg (urine) Serum $\beta_2$microglobulin: rank Hg (urine) and creatinine (urine) Serum Cystatin C: none	Regression coefficients for renal measures (log transformed) with Pb as independent variable: **creatinine (serum) = -0.026, p=0.007** **serum cystatin C = -0.056; p=0.02** **$\beta_2$microglobulin (serum) = -0.095; p=0.01** *similar results when blood or urine Cd included Differences in biomarkers by quartiles of blood Pb (µg/dL) standardized for other cofactors: Serum Creatinine (1): <2.85 (ref, n=150) 2.85-4.07 (n=149): p=NS 4.08-5.59 (n=151): p=NS **>5.59 (n=150): p =<0.01, lower than referent** Serum Creatinine (2): <28.4 (ref, n=149) 2.84-4.06 (n=151): p=NS 4.07-5.56 (n=148): p=NS **>5.56 (n=150): p =<0.01, lower than referent** Serum $\beta_2$microglobulin: <3.10 (ref, n=82); 3.10-4.14 (n=80): p=NS; 4.15-5.86 (n=81): p=NS; **>5.86 (n=81): p =<0.001, lower than referent** Serum Cystatin C: <3.09 (ref, n=81); 3.09-4.17 (n=82): p=NS; 4.18-5.86 (n=79): p=NS; >5.86 (n=81) p=0.065, lower than referent	Three renal measures decreased with increasing levels of blood Pb, in these children with low Pb levels
Prospective Factor-Litvak (1993) Yugoslavia	1,465 pregnant women in two Yugoslavian towns, one near a smelter [K. Mitrovica (n=587)], and the other considered less exposed [Pristina (n=878)] Year not stated Male = 0%	*K.Mitrovica* 26.3 (5.2) *Pristina* 26.9 (4.9)	*K.Mitrovica* 17.1 (geometric mean) *Pristina* 5.1 (geometric mean)	urinary protein	logistic regression ≥1 + proteinuria: smoking, height, age, milk consumption, gestational age, number of previous live births, meat consumption, hemoglobin trace proteinuria: smoking, ethnic group, age, milk consumption, gestational age, consumption, hemoglobin	Risk of proteinuria (in entire sample) Pb (µg/dL) ≥1+ proteinuria: Higher adjusted ORs in groups with higher blood Pb (mostly statistically significant in groups with >6.9 µg/dL Pb) trace proteinuria: Adjusted ORs mostly statistically significant in groups with >8.7µg/dL Pb	Association with blood and increased odds ratio for trace and 1+ proteinuria

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Fadrowski (2010) USA *Population may overlap with Munter (2003)*	769 adolescents aged 12-20 in NHANES Year = 1988-1994 Male = 50.4%	12-20	Median: 1.5 (IQR: 0.7-2.9)	GFR based on serum cystatin C (Filler and Lepage method) and serum creatinine (Schwartz method)	Linear regression Age, sex, race/ethnicity, urban vs rural, tobacco smoke exposure, obesity, annual household income, educational level of family reference person	Mean difference in estimated GFR (mL/min/1.73 m^2) associated with blood Pb Pb (µg/dL) / **Cystatin C-based** / Creatinine-based 1 (<1.0) / **1 (reference)** / 1 (reference) 2 (1.0-1.5) / **-1.4 (-7.4 to 4.5)** / -0.5 (-6.1 to 5.1) 3 (1.6-2.9) / **-2.6 (-7.3 to 2.2)** / -1.7 (-6.9 to 3.5) 4 (>2.9) / **-6.6 (-12.6 to -0.7)** / -1.9 (-7.4 to 3.5) p-trend / **0.009** / 0.31 Per doubling of blood Pb / **-2.9 (-5.0 to -0.7)** / -1.0 (-2.8 to 0.9)	A negative correlation between blood Pb and GFR is strongest for the cystatin C-based measure compared to the serum creatinine-based measure
Cross-sectional Fels (1998) Poland *Population may overlap with de Burbure (2006)*	112 children recruited from 3 schools in the area of Katowice, Poland. "Exposed" children (n=62, 44 boys) lived in the vicinity of Pb-producing factories and "referents" (n=50, 28 boys) lived in the same province but without Pb emission into neighborhood; Year=1995 Male = 64%	Exposed: 10.6 (1.2) Referents: 9.9 (0.4)	1995 referents : 3.9 (1.3) exposed: 13.3 (6.2) Previous screening in "exposed" only 1992 (n=21): 18.2 (2.6) 1993 (n=21): 21.0 (4.3) 1994 (n=10): 20.8 (8.9) 1994 (n=39): 17.4 (5.4)	Kidney function markers in serum (3) and urine (26). Urinary biomarkers include glomerular (5), proximal tubular enzymes (6), proximal tubular serum-derived proteins (5), proximal tubular antigens (3), distal tubular (2), collecting duct, interstitial cells (1), and general markers (4)	t test, Mann Whitney U test	Serum kidney function creatinine (↔), **β_2-microglobulin (↑, p<0.01)**, Clara cell protein (↔) Urinary Biomarkers: Glomerular: HMW (↔) , **transferrin (↑, p<0.05)**, fibronectin (↔), **6-keto-PGF1$_\alpha$ (↑, p<0.01)**, **TXB_2 (↑, p<0.01)** Enzyme, proximal tubular: αGST (↔), AAP (↔), γGT (↔), NAG_{TOTAL} (↔), **NAG B (↓, p<0.01)**, IAP (↔) Serum-derived protein, proximal tubular: α_1-microglobulin (↔), **β_2-microglobulin (↑, p<0.025)**, RBP (↔), **Clara cell protein (↑, p<0.025)**, LMW (↔) Tubular antigens: CB7 (↔), CG9 (↔), HF5 (↔) Distal tubular: :πGST (↔), **EGF (↑, p<0.001)** Collecting duct, interstitial cells: **PGE_2 (↑, p<0.01)** General markers: total protein (↔), albumin (↔), laminin (↔), LTE_4 (↔)	Children with Pb exposure have significant differences from unexposed children in urinary markers of kidney function in a pattern similar to observations in adults, but at a lower blood Pb level.
Cross-sectional Khan (2010) Pakistan	246 children recruited from families of lead smelters/battery recycle plant workers living close to the industries at Wah/Gujranwala (n=123), Pakistan and those living 30 km away from the industrial area as controls (n=123) Year not stated Male = 56%	Median (range): 4 (1-6)	Median (range): Exposed= 8.1 (1-20.9) Referents= 6.7 (1.4-13.3)	serum creatinine urea total protein	Mann Whitney test and Spearman correlation	Exposed vs Reference group comparisons total protein (↔, p=0.08) **urea (↑, p≤0.01)** **serum creatinine (↑, p≤0.01)** Correlations protein (r = -0.07; p=0.27) urea (r = 0.10, p = 0.12) serum creatinine (r = 0.13, p = 0.05)	Children with higher Pb exposure have higher serum creatinine levels

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Retrospective cohort with cross-sectional data at baseline Kim (1996) Boston, MA, USA *Population may overlap with Payton (1994) and others*	459 men randomly selected from the Normative Aging Study (healthy veterans in the greater Boston area, recruited in 1961); Years= 1979-1994 Male = 100%	56.9 (8.3) at baseline Median:56.7 Range: 37.7-87.5	9.9 (6.1) at baseline Median: 8.6 Range: 0.2-54.1	Serum creatinine concentration measured 1979-1994	Random-effects model Baseline age, time since initial visit, BMI, current smoking status, daily alcohol consumption, educational level, hypertension For change in creatinine, also includes: time between visits and current creatinine In longitudinal analysis, serum creatinine at the beginning of the follow-up interval and time between evaluations	**Serum creatinine (µmol/L) by Pb:** **β (SE)= 2.89 (1.04); p=0.005 (n=1671 observations)** **Change in serum creatinine (µmol/L) by Pb:** **β (SE)= 1.75 (1.09); p=0.11 (n=1212 observations)** **A 10-fold increase in blood Pb level predicted an increase of 7 µmol/L (95% CI: 2-12) in serum creatinine** Serum creatinine (µmol/L) by Pb tertile: ≤40 µg/dL: β (SE)= **2.78 (1.06); p=0.08** (452 subjects, 1647 observations) ≤25 µg/dL: β (SE)=**3.23 (1.18); p=0.007** (428 subjects, 1558 observations) **≤10 µg/dL: β(SE)= 5.29 (1.71); p=0.002** (141 subjects, 508 observations) Change in serum creatinine (µmol/L) by Pb tertile: ≤40 µg/dL: β (SE)= 1.96 (1.06); p= 0.07 (n=452 subjects, 1195 observations) ≤25µg/dL, β (SE)= 2.38 (1.22); p=0.05 (428 subjects, 1130 observations) **≤10µg/dL**, β (SE)=3.43 (2.24); p=0.13 (141 subjects, 367 observations)	Elevated serum creatinine was associated with long-term low-level Pb exposure
Cross-sectional Lai (2008) Taiwan	2565 subjects: 1,318 aboriginals and 1,247 non-aboriginals from Hsinyi County, a rural area of central Taiwan; Year not stated Male = 48% aboriginals 52% non-aboriginals	>40 years	Aboriginal: male:5.6 (1.4) female:5.4 (1.2) Non-Aboriginals: male: 5.3 (1.2) female: 5.3 (1.1)	Renal dysfunction Serum creatinine levels >1.2 mg/dL considered dysfunctional	Linear regression, logistic regression Age, gender, occupation, education, marital status, smoking, alcohol consumption, betel nut chewing, hypertension, high lipid level	Serum creatinine >1.2 mg/dL [Odds Ratio (95% CI)] Aboriginals: <5 µg/dL: Reference 5-7.5 µg/dL: 1.15 (0.79-1.68) >7.5 µg/dL: 2.45 (1.28-4.69) **p-trend <0.05** Non-aboriginals: <5 µg/dL: Reference 5-7.5 µg/dL: 1.24 (0.90-1.73) >7.5 µg/dL: 2.62 (1.25-5.52) **p-trend<0.05** All ≤ 7.5 µg/dL: Reference > 7.5 µg/dL: 1.92 (1.18-3.10)	Elevated serum creatinine positively associated with increased blood Pb
Prospective Lin (2003) Taiwan	202 patients with chronic renal insufficiency followed for 2 years. 64 patients with "high	baseline: 56.6 25-80 (range) "chelation	baseline: 5.3 (2.9) "chelation group" 6.1 (2.5)	primary outcome: increase in serum creatinine to 1.25 times baseline	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum	In a Cox multivariate regression analysis, baseline chelatable Pb was significantly associated with overall risk for the primary endpoint (increase in serum creatinine to 1.5 times baseline) during months 0-24 HR(95%CI) = 1.03(1.00, 1.07); p 0.03	Low level Pb associated with accelerated deterioration of renal function in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	normal" EDTA chelatable Pb levels [body lead burden, or BLB) at study start: (≥80 to <600 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=31 completed) or placebo (n=30 completed) group for months 24-51 Year not stated % male not stated	group" 57.9 (39-79) "control group" 57.6 (27-80)	"control group" 5.9 (3.0)	secondary outcome: estimated GFR following chelation therapy	creatinine to 1.5 times baseline) during the observation period. Generalized estimating equations for associations between baseline chelatable Pb or blood Pb level and longitudinal change in GFR Age, gender, baseline BMI, smoking, baseline serum creatinine, proteinuria, hypertension, hyperlipidemia, daily protein intake, and underlying renal disease	Change in glomerular filtration rate improved in patients receiving chelation therapy (2.1±5.7 ml per minute per 1.73 m^2 of body-surface area, as compared with –6.0±5.8 ml per minute per 1.73 m^2 of body-surface area in the controls, p<0.001)	chronic renal insufficiency patients
Prospective Lin (2006a) Taiwan *Population may overlap with Yu (2004)*	108 CKD patients followed for 2 years, 32 patients with "low normal" EDTA chelatable Pb levels [body lead burden at study start: ≥20 to <80 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=16) or placebo (n=16) group for months 24-51 Year not stated % male not stated	baseline: 56.2 30-80 (range) "chelation group" 58.6 (48-74) "control group" 54.8 (31-76)	baseline: 2.9 (1.4) "chelation group" 2.6 (1.0) "control group" 3.0 (1.1)	primary outcome: increase in serum creatinine to 1.25 times baseline secondary outcome: estimated GFR following chelation therapy	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum creatinine to 1.25 times baseline) during the observation period. Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	1 µg/dL higher blood Pb at baseline associated with increased risk of achieving an increase in serum creatinine to 1.25 times baseline during months 0-24 HR(95%CI) = 1.03(1.00, 1.07) **The mean GFR change in the chelation group patients was 6.6±10.7 mL/min/1.73m^2, compared with -4.6±4.3 mL/min/1.73m^2 in control group patients (*P* <0.001) at the end of the intervention period.**	Low level Pb associated with accelerated deterioration of renal insufficiency in CKD patients; less decline in function in CKD patients on EDTA chelation therapy
Prospective Taiwan Lin (2006b)	82 patients with diabetes and diabetic nephropathy followed for 1 year. 30 patients with "high normal" EDTA chelatable Pb levels [body lead burden at study start:	baseline: 60.0 33-79 (range) "chelation group" 59.5 (33-79)	baseline: 6.5 (3.4) "chelation group" 7.5 (4.6) "control group" 5.9 (2.2)	primary outcome: increase in serum creatinine to 1.25 times baseline secondary outcome: estimated GFR following chelation	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum creatinine to 1.25 times baseline) during the observation period.	1 µg/dL higher blood Pb at baseline associated with increased risk of achieving an increase in serum creatinine to 1.25 times baseline during months 0-24 HR(95%CI) = 1.01(1.01, 1.02); p = 0.0011 The mean GFR rates of decline in the chelation group patients was 5.0±5.7 mL/min/1.73m^2, compared with -11.8±7.0 mL/min/1.73m^2 in control group patients (*P*	Low level Pb associated with accelerated deterioration of renal insufficiency in diabetic patients; less decline in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	≥80 to <600 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=15 completed) or placebo (n=15 completed) group for months 13-24 Year not stated % male not stated	"control group" 57.9 (47-66)		therapy	Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	<0.001) at the end of the intervention period.	function in diabetic patients on EDTA chelation therapy
Cross-sectional Mortada (2004) Egypt	68 men (35 smokers, 33 non-smokers); Year=not stated Male = 100%	Smokers: 31.8 (range: 25-38) Non-smokers: 30 (range: 25-35)	Smokers: 14.4 (3.4) Non-smokers 10.2 (3.1)	Urine: β_2-microglobulin, NAG, γ-glutamyltransferase, and alkaline phosphatase, albumin, Serum: creatinine, β_2-microglobulin, and BUN *Study assessed exposure to Pb, Cd, and Hg*	Spearman rank correlation coefficient (r)	Smokers had higher blood Pb levels than non-smokers, but did not have elevated markers of kidney damage; and no significant correlations were found between exposure indices of Pb (blood, urine, hair) and markers of kidney damage (data not shown)	Markers of kidney damage did not correlate with Pb exposure in smokers with higher blood Pb levels than non-smokers.
Cross-sectional Munter (2003) USA *Population may overlap with Fadrowski (2010)*	NHANES III with 15,211 participants with hypertension (n=4,813) and without hypertension (n=10,398) Year = 1988-1994 Male = 48%	≥20 years	Hypertension: 4.21 (0.14) Without hypertension: 3.30 (0.10)	Elevated serum creatinine: defined as ≥99th percentile of each race-gender-specific distribution for participants aged 20-39 years without hypertension or diabetes Chronic Kidney Disease (CKD): defined as estimated GFR <60ml/min/1.73m^2	Multiple logistic regression Age, race, gender, diabetes, systolic blood pressure, smoking status, history of cardiovascular disease, BMI, alcohol consumption, household income, education level, marital status, and health insurance	Elevated Creatinine; adjusted OR (95% CI): *With Hypertension:* With each twofold higher blood Pb: 1.43 (1.20-1.72) Quartile blood Pb (µg/dL) Quartile1 (0.7-2.4); 1.00 Quartile2 (2.5-3.8); 1.47 (1.03-2.10) Quartile3 (3.9-5.9); 1.80 (1.34-2.42) Quartile4 (6.0-56.0); 2.41 (1.46-3.97) P trend<0.001 *Without hypertension*: With each twofold higher blood Pb: 1.07 (0.81-1.41) Quartile blood Pb (µg/dL); adj. OR (95% CI) Q1 (0.7-1.6); 1.00 Q2 (1.7-2.8); 1.11 (0.56-2.21) Q3 (2.9-4.6); 1.19 (0.62-2.25)	Elevated serum creatinine and chronic kidney disease (CKD) is positively associated with blood Pb in subjects with hypertension only

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
						Q4 (4.7-52.9); 1.09 (0.53-2.22) P trend= 0.79 <u>Elevated Creatinine; adjOR (95% CI):</u> *Hypertension* With each twofold higher blood Pb: 1.38 (1.15-1.66) Quartile (blood Pb (µg/dL) Q1 (0.7-2.4); 1.00 Q2 (2.5-3.8); 1.44 (1.00-2.09) Q3 (3.9-5.9); 1.85 (1.32-2.59) Q4 (6.0-56.0); 2.60 (1.52-4.45) P trend<0.001 *Without hypertension*: With each twofold higher blood Pb: 1.04 (0.72-1.38) Quartile blood Pb (µg/dL); adjusted OR (95% CI) Q1 (0.7-1.6); 1.00 Q2 (1.7-2.8); 0.90 (0.37-2.16) Q3 (2.9-4.6); 1.00 (0.45-2.22) Q4 (4.7-52.9); 1.09 (0.41-2.89) P trend= 0.36	
Cross-sectional Muntner (2005) USA *Population may overlap with Navas-Acien (2009)*	9,961 adults from NHANES Year = 1999-2002 % male not stated	NHANES 1999-2002: 18-75 years	NHANES 1999-2002: 1.64 (95% CI: 1.59-1.68)	Chronic kidney disease (GFR <60 mL/min)	Multiple logistic regression Age, race/ethnicity, gender, diabetes, smoking status, alcohol, BMI, education, and health insurance	<u>NHANES 1999-2002:</u> Adjusted OR (95% CI) of chronic kidney disease by quartile of blood Pb Q1: <1.06 µg/dL (prevalence 1.8%); 1.00 (Reference) Q2: 1.06-1.63 µg/dL (prevalence 3.4%); Adjusted OR = 1.49 (0.75-2.98) Q3: 1.63-2.47 µg/dL (prevalence 5.6%); Adjusted OR =1.89 (1.09-3.30) Q4: ≥2.47 µg/dL (prevalence 8.1%); Adjusted OR = 2.72 (1.47-5.04) P trend=<0.001	Increased risk of CKD with blood Pb ≥1.63 µg/mL
Cross-sectional Navas-Acien (2009) USA *Population may overlap with Muntner (2005)*	14,778 adults from the NHANES Year = 1999-2006 % male not stated	≥20	1.58 (geometric mean)	Albuminuria (≥30 mg/g creatinine), reduced e stimated GFR (<60 mL/minute/1.73 m^2) Described in study but not summarized here are kidney	Logistic regression; Model 3: Survey year, age, race/ethnicity, gender, smoking status, alcohol intake, BMI, education, cotinine, hypertension, diabetes mellitus, menopausal status, and	Albuminuria, OR (95% CI) by quartile of blood Pb (µg/dL) (median) Q1: ≤1.1; 1.0 (Reference) Q2: >1.1-1.6; adjusted OR = 0.83(0.66-1.04) Q3: >1.6-2.4; adjusted OR = 0.92 (0.76-1.12) Q4: >2.4; adjusted OR = 1.19 (0.96-1.47) **p-trend<0.001** Reduced estimated GFR, OR (95% CI) by quartile of	Increased risk of reduced estimated GFR in highest quartile for Pb exposure; significant trend for albuminuria

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
				effects related to Cd	blood Cd	blood Pb (µg/dL) (median) Q1: ≤1.1; 1.0 (Reference) Q2: >1.1-1.6; adjusted OR = 1.10 (0.80-1.51) Q3: >1.6-2.4; adjusted OR = 1.36 (0.99-1.85) **Q4: >2.4; adjusted OR = 1.56 (1.17-2.08)** **p-trend<0.001** *Association with estimated GFR stronger when people more highly exposed to both Pb and Cd compared to those less exposed	
Cross-sectional Payton (1994) Boston, MA, USA *Population may overlap with Kim (1996) and others*	744 adults participating in the Normative Aging Study; Year= 1988-1991 Male = 100%	64 (7.4)	8.1 (3.9)	Log- transformed (ln) creatinine clearance (both measured and estimated from serum creatinine)	Multivariate linear regression Age, BMI, analgesic & diuretic use, alcohol consumption, smoking status, systolic/diastolic blood pressure	Rate of ln creatinine clearance (mL/min) was significantly and negatively associated with increasing levels of ln blood: Adjusted β between ln Pb and ln measured creatinine clearance =-0.0403 (0.0198) µg/dl; p-value= 0.0426 A 10µg/dl rise in blood Pb was associated with a decrease in creatinine clearance rate of 10.4 mL/minute	Low-level Pb associated with decreased renal function
Cross-sectional Pocock (1984) England	7,364 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	40-59 (mean not reported)	<12.4 – 37.3 (mean not reported) *limits utility of the study in this evaluation	Serum creatine, urate, urea	Statistical methods not reported but statistics were presented as correlation coefficients (β) Alcohol consumption	β for blood Pb and log transformed urine level: serum urate (β = 0.06)* serum urea (β = -0.05)* serum creatinine: no association (β=0.00) Authors state that the magnitude of the changes are small and unlikely to be of biological importance	Lack of information on blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Satarug (2004a) Thailand	118 Thai adults; Year not stated Male = 45%	*Men,* 36.7 (range: 21-57) *Women,* 38.1 (range: 23-55)	Males: 0.42 Females: 0.3 (reported as "serum" Pb)	Serum creatinine, urinary NAG and β2-microglobulin, BUN, total urinary protein,	Spearman rank correlation adjusted for urine cadmium	correlations with kidney filtration markers and urine Pb (correlations with blood Pb not reported) NAG (r = 0.39; p < 0.001) protein (r = 0.09, p = 0.47) β2-microglobulin (r = 0.16, p = 0.19)	Lack of information on correlations with blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Satarug (2004b) Thailand	96 Thai men subdivided into nonsmokers (n = 53), current smokers (n = 27), and ex-smokers (n = 16) Year not stated Male = 100%	*Non-smokers,* 36.7 (range: 21-57) *Current Smokers,* 35.8 (range: 19-53) *Ex-Smokers,* 38.5	*Non-smokers,* 0.42 (0.54) *Current Smokers,* 0.9 (0.12) *Ex-Smokers,* 0.61 (0.63)	Serum creatinine, urinary NAG and β2-microglobulin, BUN, total urinary protein, urinary Cd	Spearman rank correlation	correlations with kidney filtration markers and urine Pb (correlations with blood Pb not reported) *Non-smokers,* NAG (r = 0.08; p=0.27) protein (r = 0.22, p = 0.06) β2-microglobulin (r = 0.12, p = 0.19) *Current Smokers,* NAG (r = -0.02; p=0.47)	Lack of information on correlations with blood Pb levels in this study limits the utility

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
		(range: 20-57)				protein (r = 0.49, p = 0.004) β2-microglobulin (r = 0.09, p = 0.32) *Ex-Smokers,* NAG (r = 0.27; p < 0.16) protein (r = -0.14, p = 0.31) β2-microglobulin (r = 0.39, p = 0.06)	
Retrospective Shadick (2000) Boston, MA, USA *Population may overlap with Payton (1994) and others*	777 participants in all male Normative Aging Study Year = 1991 and 1996 Male = 100%	66.9 (7.3)	5.9 (3.5)	Uric acid	Logistic regression Age, BMI, diastolic blood pressure, alcohol intake, serum creatinine	Significant association between patella Pb and uric acid (β= 0.0007 [95% CI: 0.001, 0.013]; p = 0.02); borderline significant associations between tibia (p = 0.06) and blood Pb (p = 0.1) and uric acid were also observed.	Lack of information on correlations with blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Staessen (1990) London, England	531 adult London civil servants; Year not stated Male = 75%	37-58	Male (n=398): 12.4 Female (n=133): 10.2	Serum creatinine	t-test for comparison of means and linear multiple regression analysis (step wise)	In male, significant correlation between serum creatinine and log blood Pb (r = 0.10, p=0.04)* In female, no correlation with serum creatinine and log blood Pb (r=0.03, p= NS) The predicted increase in serum creatinine concentration per 25% increase in blood Pb was β = 0.6 µmol/L (95% CI, -0.2, 1.36). *The association was no longer significant after excluding two subjects from the analysis who had serum creatinine concentrations exceeding 180 µmol/L (2 mg/dL).	Blood Pb was associated with increased serum creatinine in men when 2 individuals with >180µmol/L creatinine were included. Blood Pb was not associated with serum creatinine in women or men when the individuals with high serum creatinine were excluded.
Cross-sectional Staessen (1992) Belgium	1,981 residents participating in the ≥8 years study; Year= 1985-1989 Male = 48%	48 (16) (range: 20-88)	male: 11.4 (range 2.3-72.5) female: 7.5 (range 1.7-60.3)	<u>Impaired renal function:</u> creatinine clearance <43 ml/min in non-diabetic women and <52 ml/min in non-diabetic men Serum creatinine; urine creatinine; creatinine clearance	Analysis of variance, single and multiple linear regression, and logistic-regression Age, diabetes, use of analgesic and diuretic drugs	<u>β (±SE) with ln blood Pb:</u> Ln creatinine clearance (mL/min, measured) male: -13.1 (±4.0); female: -9.5 (±4.4) Ln β2-microglobulin (mg/L) male: 0.04 (±0.02); female: -0.01 (±0.02) Ln serum creatinine (mg/dL) male: 0.01 (±0.01); female: 0.01 (±0.01) adjOR (95%CI) for 10-fold increase in blood Pb and impaired renal function = 3.76 (1.37, 10.4)	10-fold increase in blood Pb associated with reduction of 10 (female) to 13 (male) ml/min creatinine clearance

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Staessen (2001) Belgium	200 children aged 17 (Pb exposed n=42 from Wilrijk and n=58 from Hoboken both considered Pb- and chemical-industrial areas; n=100 referent); Year=1999 Male = referent=40%; Wilrijk=50%; Hoboken=33%	17	Referent 1.49µg/dL Wilrijk 1.8µg/dL Hoboken 2.7µg/dL	serum cystatin C and urinary β2 microglobulin	ANOVA and Fisher's exact test, linear regression and logistic regression Adjustments included sex, smoking, and initial urinary pH (for β2 microglobulin)	Geometric Mean Blood Pb: Referent 1.49µg/dL Wilrijk 1.8µg/dL; p=0.04 to referent Holboken 2.7µg/dL; p<0.0001 to referent Serum cystatin C (mg/L): Referent 0.65 Wilrijk 0.63; p=NS Holboken 0.71; p=<0.0001 Urinary β2 microglobulin (µg/mmol creatinine): Referent 5.22 Wilrijk 5.30; p=NS Holboken 9.09; p=<0.0001	Serum cystatin-C and β2 microglobulin were higher in children living in areas with higher blood Pb (2.7µg/dL) compared to referents
Prospective cohort with cross-sectional data at baseline Tsaih (2004) Boston, MA, USA *Population may overlap with Payton (1994) and others*	448 men participating in the Normative Aging Study Year recruited during 1991-1995 were followed for 6 years Male = 100%	At baseline: 66 (6.6) At baseline: 72 (6.5)	Baseline: 6.5 (4.2) Followup: 4.5 (2.5)	Serum creatinine	Multiple linear regression Age, BMI, baseline serum creatinine (SCr), SCr squared, diabetic status, hypertensive status, smoking history, alcohol consumption, and ue of analgesic medication and diuretic medication	β(SE) of baseline blood Pb with change in serum creatinine: diabetics (n=26): 0.076 (0.023); p-value = <0.05 non-diabetics (n=422): 0.006 (0.005); p-value = NS hypertensive (n=115): 0.008 (0.010); p-value = NS normotensives (n=333): 0.009 (0.006); p-value = NS	Significant associations blood Pb and change in serum creatinine in diabetics
Cross-sectional Wu (2003) Boston, MA, USA *Population may overlap with Payton (1994) and others*	709 adults (100% male) participating in the Normative Aging Study; objective of study was to investigate whether an *ALAD* polymorphism has a modifying effect on the association of blood or bone Pb level with uricemia and indices of renal function; Year= 1991-1995 Male = 100%	67 (7.4) years	6.2 (4.1)	Serum creatinine, serum uric levels, estimated creatinine clearance	Multiple linear regression; Age, BMI, hypertension, smoking status, alcohol ingestion, analgesic medication use	<u>Estimated creatinine clearance (mL/min)</u> Significant negative association between patella Pb and estimated creatinine clearance: Patella: β=-0.069; p-value=0.024 Tibia: β=-0.078; p-value=0.082 <u>Serum creatinine (mg/dL)</u> Bone Pb levels were not associated with serum creatinine Patella: β=0.0004; p-value=0.41 Tibia: β=0.0006; p-value= 0.354 <u>Uric Acid (mg/dL)</u> Patella: β=0.005; p-value=0.078 Tibia: β=0.005; p-value=0.190 Authors state that no significant association was detected between blood Pb or its interaction with genotype to serum uric acid.	Creatinine clearance inversely significantly associated with patella Pb, not blood Pb. Serum creatinine and uric acid not significantly associated with any lead measure.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Prospective Yu (2004) Taiwan *Population may overlap with Lin (2006a)*	121 CKD patients (77% male) followed for 4 years, patients were divided into 2 groups based on EDTA chelatable Pb levels (body lead burden (BLB) at study start: "low normal" (<80 µg/72 h; n=58) and "high normal" (≥80 to <600 µg/72 h; n=63) Year not stated % male not stated	Baseline= 25-82 (range) "low normal" BLB= 54.8 (mean) "high normal" BLB= 59 (mean)	baseline: 4.2 (2.2) "low normal" BLB: 3.4 (1.3) "high normal" BLB: 4.9 (2.6)	Estimated GFR (MDRD equation)	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (doubling of serum creatinine over the 4 yr study period or need for hemodialysis) during the observation period. Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	1 µg/dL higher blood Pb at baseline associated with a 4.0 mL/min/1.73 m^2 reduction in eGFR over 4 years Fifteen patients in the "high-normal" BLB group reached the primary endpoint (doubling of serum creatinine over the 4 yr study period or need for hemodialysis) compared to only two in the "low-normal" group (p = 0.001 by Kaplan-Meier analysis)	Low level Pb associated with accelerated deterioration of renal insufficiency in CKD patients

Abbreviations: AAP – alanine aminopeptidase; ALAD – γ-aminolevulinic acid dehydratase; ANOVA – analysis of variance; As – arsenic; BMI - body mass index; BLB – body lead burden; BUN – blood urea nitrogen; Cd – cadmium; CI – confidence interval; CKD - chronic kidney disease; CRI - chronic renal insufficiency; EDTA – edetate calcium disodium; EGF – epidermal growth factor; GFR - glomerular filtration rate; αGST – α-glutathione-S-transferase; γGT – γ-glutamyl transferase; Hg – mercury; HMW –high molecular weight; HR – hazard ratio; IQR - interquartile range; IAP – intestine alkaline phosphatase; ln – natural log; min – minute; LMW – low molecular weight; LTE_4 – leukotriene E_4; NAG - N-acetyl-β-D-glucosaminidase; NAG B – isoform B of NAG; NHANES – National Health and Nutrition Examination Survey; NS – not significant; OR – odds ratio; Pb – lead; PG - prostaglandin (i.e. PGE_2 , $PGF_{1\alpha}$); RBP - retinol binding protein; SE – standard error; TXB_2 – thromboxane; UI – international unit; vs – versus

References:

Akesson A, Lundh T, Vahter M, Bjellerup P, Lidfeldt J, Nerbrand C, Samsioe G, Stromberg U, Skerfving S. 2005. Tubular and glomerular kidney effects in Swedish women with low environmental cadmium exposure. *Environ Health Perspect* 113(11): 1627-1631.

Alfven T, Jarup L, Elinder CG. 2002. Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. *Environ Health Perspect* 110(7): 699-702.

Bernard AM, Vyskocil A, Roels H, Kriz J, Kodl M, Lauwerys R. 1995. Renal effects in children living in the vicinity of a lead smelter. *Environ Res* 68(2): 91-95.

de Burbure C, Buchet JP, Bernard A, Leroyer A, Nisse C, Haguenoer JM, Bergamaschi E, Mutti A. 2003. Biomarkers of renal effects in children and adults with low environmental exposure to heavy metals. *J Toxicol Environ Health A* 66(9): 783-798.

de Burbure C, Buchet JP, Leroyer A, Nisse C, Haguenoer JM, Mutti A, Smerhovsky Z, Cikrt M, Trzcinka-Ochocka M, Razniewska G, Jakubowski M, Bernard A. 2006. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. *Environ Health Perspect* 114(4): 584-590.

Factor-Litvak P, Stein Z, Graziano J. 1993. Increased risk of proteinuria among a cohort of lead-exposed pregnant women. *Environ Health Perspect* 101(5): 418-421.

Fadrowski JJ, Navas-Acien A, Tellez-Plaza M, Guallar E, Weaver VM, Furth SL. 2010. Blood lead level and kidney function in US adolescents: The Third National Health and Nutrition Examination Survey. *Arch Intern Med* 170(1): 75-82.

Fels LM, Wunsch M, Baranowski J, Norska-Borowka I, Price RG, Taylor SA, Patel S, De Broe M, Elsevier MM, Lauwerys R, Roels H, Bernard A, Mutti A, Gelpi E, Rosello J, Stolte H. 1998. Adverse effects of chronic low level lead exposure on kidney function--a risk group study in children. *Nephrol Dial Transplant* 13(9): 2248-2256.

Khan DA, Qayyum S, Saleem S, Ansari WM, Khan FA. 2010. Lead exposure and its adverse health effects among occupational worker's children. *Toxicol Ind Health* 26(8): 497-504.

Kim R, Rotnitsky A, Sparrow D, Weiss S, Wager C, Hu H. 1996. A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aging Study. *Jama* 275(15): 1177-1181.

Lai LH, Chou SY, Wu FY, Chen JJ, Kuo HW. 2008. Renal dysfunction and hyperuricemia with low blood lead levels and ethnicity in community-based study. *Sci Total Environ* 401(1-3): 39-43.

Lin JL, Lin-Tan DT, Hsu KH, Yu CC. 2003. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. *N Engl J Med* 348(4): 277-286.

Lin JL, Lin-Tan DT, Li YJ, Chen KH, Huang YL. 2006a. Low-level environmental exposure to lead and progressive chronic kidney diseases. *Am J Med* 119(8): 707 e701-709.

Lin JL, Lin-Tan DT, Yu CC, Li YJ, Huang YY, Li KL. 2006b. Environmental exposure to lead and progressive diabetic nephropathy in patients with type II diabetes. *Kidney Int* 69(11): 2049-2056.

Mortada WI, Sobh MA, El-Defrawy MM. 2004. The exposure to cadmium, lead and mercury from smoking and its impact on renal integrity. *Med Sci Monit* 10(3): CR112-116.

Muntner P, He J, Vupputuri S, Coresh J, Batuman V. 2003. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. *Kidney Int* 63(3): 1044-1050.

Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V. 2005. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. *Arch Intern Med* 165(18): 2155-2161.

Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, Weaver V. 2009. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. *Am J Epidemiol* 170(9): 1156-1164.

Payton M, Hu H, Sparrow D, Weiss ST. 1994. Low-level lead exposure and renal function in the Normative Aging Study. *Am J Epidemiol* 140(9): 821-829.

Pocock SJ, Shaper AG, Ashby D, Delves T, Whitehead TP. 1984. Blood lead concentration, blood pressure, and renal function. *Br Med J (Clin Res Ed)* 289(6449): 872-874.

Satarug S, Nishijo M, Ujjin P, Vanavanitkun Y, Baker JR, Moore MR. 2004a. Evidence for concurrent effects of exposure to environmental cadmium and lead on hepatic CYP2A6 phenotype and renal function biomarkers in nonsmokers. *Environ Health Perspect* 112(15): 1512-1518.

Satarug S, Ujjin P, Vanavanitkun Y, Nishijo M, Baker JR, Moore MR. 2004b. Effects of cigarette smoking and exposure to cadmium and lead on phenotypic variability of hepatic CYP2A6 and renal function biomarkers in men. *Toxicology* 204(2-3): 161-173.

Shadick NA, Kim R, Weiss S, Liang MH, Sparrow D, Hu H. 2000. Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the normative aging study. *The Journal of rheumatology* 27(7): 1708-1712.

Staessen J, Yeoman WB, Fletcher AE, Markowe HL, Marmot MG, Rose G, Semmence A, Shipley MJ, Bulpitt CJ. 1990. Blood lead concentration, renal function, and blood pressure in London civil servants. *Br J Ind Med* 47(7): 442-447.

Staessen JA, Lauwerys RR, Buchet JP, Bulpitt CJ, Rondia D, Vanrenterghem Y, Amery A. 1992. Impairment of renal function with increasing blood lead concentrations in the general population. The Cadmibel Study Group. *N Engl J Med* 327(3): 151-156.

Staessen JA, Nawrot T, Hond ED, Thijs L, Fagard R, Hoppenbrouwers K, Koppen G, Nelen V, Schoeters G, Vanderschueren D, Van Hecke E, Verschaeve L, Vlietinck R, Roels HA. 2001. Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. *Lancet* 357(9269): 1660-1669.

Tsaih SW, Korrick S, Schwartz J, Amarasiriwardena C, Aro A, Sparrow D, Hu H. 2004. Lead, diabetes, hypertension, and renal function: the normative aging study. *Environ Health Perspect* 112(11): 1178-1182.

Wu MT, Kelsey K, Schwartz J, Sparrow D, Weiss S, Hu H. 2003. A delta-aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: the normative aging study. *Environ Health Perspect* 111(3): 335-341.

Yu CC, Lin JL, Lin-Tan DT. 2004. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. *J Am Soc Nephrol* 15(4): 1016-1022.